



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING CONTINUATION/DIVISIONAL
APPLICATION UNDER 37 C.F.R. § 1.53(b)

Box PATENT APPLICATION

Assistant Commissioner for Patents
Washington, D.C. 20231



Sir:

This is a request for filing a ☐ continuation ☒ divisional application under 37 C.F.R.
§ 1.53(b) of pending Application No. 08/930,796 filed on November 24, 1997, for
HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC
COMPOSITIONS CONTAINING THEM AND USES THEREOF, by the following named
inventor(s):

- (a) Full Name Philippe DIAZ
- (b) Full Name Bruno CHARPENTIER
- (c) Full Name _____

- ☒ The entire disclosure of the prior application from which a copy of the oath or declaration is
supplied herewith is considered as being part of the disclosure of the accompanying
application and is hereby incorporated by reference therein.
- ☐ This application is being filed by less than all the inventors named in the prior application.
In accordance with 37 C.F.R. 1.63(d)(2), the Commissioner is requested to delete the
name(s) of the following person or persons who are not inventors of the invention being
claimed in this application.

- (a) Full Name _____
- (b) Full Name _____
- (c) Full Name _____

1. ☒ Enclosed is a copy of the prior Application No. 08/930,796 as originally filed on
November 24, 1997, including copies of the specification, claims, drawings and the
executed oath or declaration as filed.
2. ☐ Enclosed is a revised prior application and a copy of the prior executed oath or
declaration as filed. No new matter has been added to the revised application.

3. ☐ _____ statement(s) claiming small entity status ☐ are enclosed ☐ were filed in prior Application No. __, filed on __.
4. ☒ The filing fee is calculated below ☒ and in accordance with the enclosed preliminary amendment:

CLAIMS					
	NO. OF CLAIMS		EXTRA CLAIMS	RATE	FEE
Basic Application Fee					\$760.00
Total Claims	10	MINUS 20 =	0	x \$18.00 =	0.00
Independent Claims	1	MINUS 3 =	0	x \$78.00 =	0.00
If multiple dependent claims are presented, add \$260.00					0.00
Total Application Fee					760.00
If small entity status is claimed, subtract 50% of Total Application Fee					0.00
Add Assignment Recording Fee of \$40.00 if Assignment document is enclosed					0.00
TOTAL APPLICATION FEE DUE					760.00

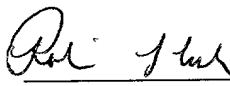
5. ☐ Charge \$ _____ to Deposit Account No. 02-4800 for the fee due.
6. ☒ A check in the amount of \$ 760.00 is enclosed for the fee due.
7. ☒ The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§ 1.16, 1.17 and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800. This paper is submitted in triplicate.
8. ☒ Cancel in this application original claims 2-27 of the prior application before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)
9. ☒ Amend the specification by inserting before the first line the sentence: --This application is a ☐ continuation, ☒ divisional, of Application No. 08/930,796, filed November 24, 1997; which in turn is a 371 of Application No. PCT/FR97/00217, filed February 4, 1997.--
10. ☐ Transfer the drawings from the pending prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate of this paper is

enclosed for filing in the prior application file. (May only be used if signed by person authorized under 37 C.F.R. § 1.138 and before payment of issue fee.)

11. ☐ New drawings are enclosed.
12. ☒ Priority of Application No. 96/01424 filed on February 6, 1996 in France (country) is claimed under 35 U.S.C. § 119.
- ☒ The certified copy of the priority application
☐ is enclosed
☒ was filed in prior Application No. PCT/FR97/00217, filed on February 4, 1997.
☐ has not yet been filed.
13. ☒ A preliminary amendment is enclosed.
14. ☒ The Assignee of record is Centre International de Recherches Dermatologiques Garlderma.
15. ☒ Also enclosed Request for Listing of References Considered by Examiner.
16. ☒ The power of attorney in the prior application is to Norman H. Stepno.
- a. ☒ The power appears in the original papers in the prior application.
- b. ☐ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.
- c. ☒ Recognize as Associate Attorney Robin L. Teskin, Reg. No. 35,030.
- d. ☒ Address all future communications to: (May only be completed by applicant, or attorney or agent of record.)

Norman H. Stepno
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404

August 23, 1999
Date

By: 
Robin L. Teskin
Registration No. 35,030

ADDRESS OF
SIGNATOR:

BURNS, DOANE, SWECKER & MATHIS, L.L.P.
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- ☐ inventor(s)
☐ assignee of complete interest
☐ attorney or agent of record
☒ filed under 37 C.F.R. § 1.34(a)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of)
Philippe DIAZ et al.) Group Art Unit: Unassigned
Application No. Unassigned) Examiner: Unassigned
Filed: August 23, 1999)
For: HETEROCYCLIC COMPOUNDS,)
PHARMACEUTICAL AND COSMETIC)
COMPOSITIONS CONTAINING THEM)
AND USES THEREOF)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please first amend the above-identified application as follows:

IN THE SPECIFICATION

Page 1, line 2, insert "BRIEF SUMMARY OF THE INVENTION";

Page 1, after line 26, insert the following text:

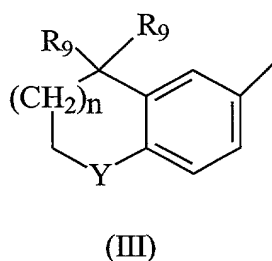
--BRIEF DESCRIPTION OF THE FIGURES

Figure 1 schematically depicts a reaction scheme for synthesis of compounds according to the invention; and

Figure 2 also schematically depicts a reaction scheme for synthesis of compounds according to the invention.

DETAILED DESCRIPTION OF THE INVENTION--

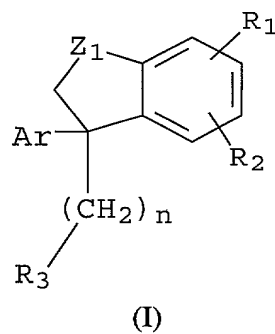
Page 2, after line 5, delete structure (III), and substitute the following therefor:



IN THE CLAIMS

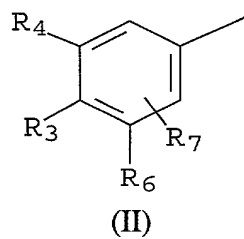
Please cancel Claim 1 and insert the following new Claims 28 to 37:

~~--28.~~ A method for treating a dermatological condition comprising administering a therapeutically effective amount of a compounds, which have the general formula (I) below:

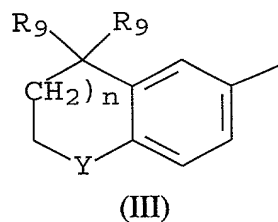


in which:

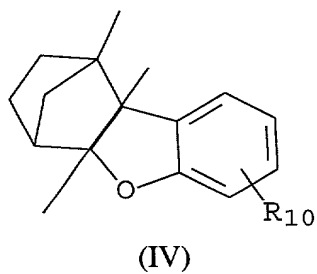
- Ar represents
- either the radical of formula (II) below:



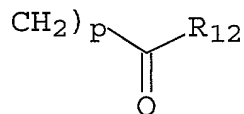
- or the radical of formula (III) below:



- or the radical of formula (IV) below:



- R_1 represents an atom or a radical chosen from
 - (i) the $-CH_3$ radical,
 - (ii) the radical $-(CH_2)_p-O-R_{11}'$
 - (iii) a radical $-OR_{11}'$
 - (iv) a radical



(v) a radical $-\text{S}(\text{O})_t\text{R}_{13}$,

R_{11} , R_{12} , R_{13} , p and t having the meanings given below,

- R_2 represents a hydrogen atom, a halogen atom, an alkyl radical or the radical -
 OR_{11} ,

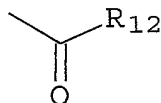
R_{11} having the meaning given below,

- R_3 represents an atom or a radical chosen from:

(i) an atom or a radical chosen from a hydrogen atom, an alkyl radical, an alkenyl radical, an alkynyl radical, an aryl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical, a cyano radical or a radical $-\text{O}-\text{R}_{11}$,

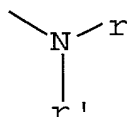
R_{11} having the meaning given below,

(ii) a radical



R_{12} having the meaning given below,

(iii) a radical



r and r' having the meaning given below,

- Z_1 represents O, S or NR' ,
- m is an integer between 0 and 10, it being understood in all of the preceding text that: R_4 , R_5 , R_6 and R_7 , which may be identical or different, are chosen from:

(i) a hydrogen atom,

(ii) an alkyl radical having at least 4 carbon atoms, among

which the carbon attached to the phenyl radical is substituted with at least two carbon atoms,

(iii) a cycloalkyl radical,

(iv) a radical $-(Z_2)_n-(CH_2)_q-CO-R_{12}$,

(v) a radical $-Z_3-R_{11}$,

with at least one of the radicals R_4 , R_5 , R_6 and R_7 being an alkyl radical as defined in (ii) or a cycloalkyl radical (iii),

$Z_2, Z_3, R_{11}, R_{12}, n$ and q having the meanings given below,

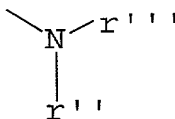
R_8 and R_9 represent lower alkyl radicals,

R_{10} represents a lower alkyl radical, a radical $-OR_{11}$ or a polyether radical,

R_{11} , which may be identical or different, represents a hydrogen atom, a lower alkyl radical, an aryl radical, an aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical or a lower acyl radical,

R_{12} , which may be identical or different, represents:

- (a) a hydrogen atom, an alkynyl radical, an alkenyl radical, an alkyl radical or a heterocycle,
- (b) a radical



R'' and R''' having the meaning given below

- (c) a radical $-OR_{13}$

R_{13} , which may be identical or different, represents a hydrogen atom, an alkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical or a sugar, amino acid or peptide residue,

R' , which may be identical or different, represents a protecting group for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical or an optionally substituted aryl radical or an amino acid, peptide or sugar residue,

r and r' , which may be identical or different, represent protecting groups for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

r'' and r''' , which may be identical or different, represent a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

Y represents $C(R_9)_2$, O, S, Nr' , CHOH, CO, SO or SO_2 ,

Z_2 represents O, S or NR' ,

Z_3 represents O or S,

n , which may be identical or different, is equal to 0 or 1; p , which may be identical or different, is equal to 0, 1, 2 or 3; t is equal to 0, 1, 2 or 3; q is an integer between 0 and 10,

as well as the salts thereof and the optical and geometrical isomers thereof.

29. The method of Claim 28, wherein said dermatological condition is selected from the following: a keratinization disorder which effects differentiation and proliferation; a keratinization disorder which is not associated with differentiation and proliferation; a keratinization disorder having an inflammatory and/or immunoallergic component; psoriasis; dermal or epidermal proliferation; bullosis and collagen disorders; light-induced and chronological aging of the skin; actinic keratosis and pigmentation; chronological or actinic agent associated pathology; stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids; cicatrization disorders; vibicies; sebaceous associated disorders; viral related skin disorders; alopecia; dermatological conditions having an immunological component; and skin disorders attributable to exposure to UV radiation.

30. The method of Claim 29, wherein the treated dermatological condition is psoriasis and said psoriasis is selected from a group consisting of cutaneous, mucous or ungual psoriasis and psoriatic rheumatism.

31. A method of treating a cancerous of precancerous state comprising administering a therapeutically amount of a compound according to Claim 28.

32. A method for treating a cardiovascular associated conditions selected from arteriosclerosis or hypertension comprising administering a therapeutically effective amount of a compound according to Claim 28.

33. A method for treating insulin independent diabetes comprising administering a therapeutically effective amount of a compound according to Claim 28.

34. The method according to Claim 28, wherein said dermatological condition associated with differentiation of proliferation is selected from the group consisting of common acnes, comedones, polymorphonuclear leukocytes, acne rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acne, medication-induced acne and occupational acne.--

35. The method according to Claim 28, wherein said keratinization disorder is selected from the group consisting of ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias, leucoplasiform states, and cutaneous or mucous (buccal) lichen.

36. The method according to Claim 28, wherein said dermatological condition is a dermal or epidermal proliferation selected from the group consisting of a common wart, flat wart, verruciform epidermodysplasia, oral or florid papillomatosis, and proliferations induced by ultraviolet radiation.

37. A method for treating an ophthalmological disorder comprising administering a therapeutically effective amount of a compound according to Claim 1.--

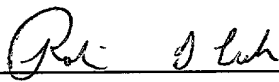
REMARKS

Claims 1 to 27 have been cancelled, and rewritten as new Claims 28 to 37, in order to better emphasize the preferred embodiment of the invention.

Favorable consideration on the merits is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 
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Date: August 23, 1999

HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND
COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF

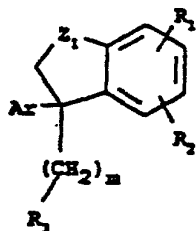
The invention relates to heterocyclic biaryl compounds as novel and useful industrial products. It
5 also relates to the use of these novel compounds in pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.

The compounds according to the invention have
10 pronounced activity in the fields of cell proliferation and differentiation, and find applications more particularly in the topical and systemic treatment of dermatological complaints associated with a disorder of keratinization, dermatological (or other) complaints
15 with an inflammatory and/or immunoallergic component, and dermal or epidermal proliferations, these being either benign or malignant. These compounds may also be used in the treatment of degenerative diseases of connective tissue, to combat ageing of the skin, both
20 light-induced and chronological ageing, and to treat disorders of cicatrization. They moreover find an application in the ophthalmological field, in particular in the treatment of corneopathies.

The compounds according to the invention may
25 also be used in cosmetic compositions for body and hair hygiene.

The compounds according to the invention may

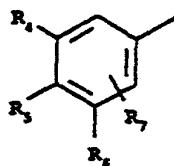
be represented by the general formula (I) below:



(I)

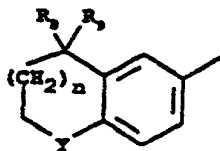
in which:

- Ar represents
- . either the radical of formula (II) below:



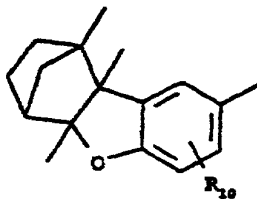
(II)

- 5 . or the radical of formula (III) below:



(III)

- . or the radical of formula (IV) below:

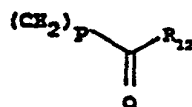


(IV)

- R_1 represents an atom or a radical chosen from

- (i) the $-\text{CH}_3$ radical,
- (ii) the radical $-(\text{CH}_2)_p-\text{O}-R_{11}$,
- (iii) a radical $-\text{OR}_{11}$,
- (iv) a radical

5



- (v) a radical $-\text{S}(\text{O})_t R_{13}$,

R_{11} , R_{12} , R_{13} , p and t having the meanings given below,

- R_2 represents a hydrogen atom, a halogen atom, an alkyl radical or the radical $-\text{OR}_{11}$,

10

R_{11} having the meaning given below,

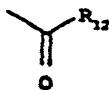
- R_3 represents an atom or radical chosen from:

- (i) an atom or radical chosen from a hydrogen atom, an alkyl radical, an alkenyl radical, an alkynyl radical, an aryl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical, a cyano radical or a radical $-\text{O}-R_{11}$,

15

R_{11} having the meaning given below,

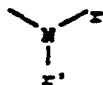
- (ii) a radical



20

R_{12} having the meaning given below,

- (iii) a radical



r and r' having the meaning given below,

- Z_1 represents O, S or NR' ,

- m is an integer between 0 and 10,

it being understood in all of the preceding text that:

5 R_4 , R_5 , R_6 and R_7 , which may be identical or different, are chosen from:

(i) a hydrogen atom,

(ii) an alkyl radical having at least 4 carbon atoms, among which the carbon attached to the
10 phenyl radical is substituted with at least two carbon atoms,

(iii) a cycloalkyl radical,

(iv) a radical $-(Z_2)_n-(CH_2)_q-CO-R_{12}$,

(v) a radical $-Z_3-R_{11}$,

15 with at least one of the radicals R_4 , R_5 , R_6 and R_7 being an alkyl radical as defined in (ii) or a cycloalkyl radical (iii),

Z_2 , Z_3 , R_{11} , R_{12} , n and q having the meanings given below,

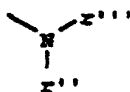
20 R_8 and R_9 represent lower alkyl radicals,

R_{10} represents a lower alkyl radical, a radical $-OR_{11}$ or a polyether radical,

R_{11} , which may be identical or different, represents a hydrogen atom, a lower alkyl radical, an aryl radical, an aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical or a lower acyl radical,

R_{12} , which may be identical or different, represents:

- (a) a hydrogen atom, an alkynyl radical, an alkenyl radical, an alkyl radical or a heterocycle,
- (b) a radical



r'' and r''' having the meaning given below

- (c) a radical $-OR_{13}$

R_{13} , which may be identical or different, represents a hydrogen atom, an alkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, an optionally substituted aryl or aralkyl radical or a sugar, amino acid or peptide residue,

R' , which may be identical or different, represents a protecting group for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid,

peptide or sugar residue,

r and r', which may be identical or different,
 represent protecting groups for amine functions, a
 hydrogen atom, a lower alkyl radical, a polyether
 5 radical, an optionally substituted aryl radical or an
 amino acid, peptide or sugar residue, or alternatively,
 taken together, form a heterocycle,

r'' and r''', which may be identical or different,
 represent a hydrogen atom, a lower alkyl radical, a
 10 polyether radical, an optionally substituted aryl
 radical or an amino acid, peptide or sugar residue, or
 alternatively, taken together, form a heterocycle,

Y represents $C(R_9)_2$, O, S, Nr' , $CHOH$, CO , SO or SO_2 ,

Z_2 represents O, S or NR' ,

15 Z_3 represents O or S,

n, which may be identical or different, is equal to 0
 or 1; p, which may be identical or different, is equal
 to 0, 1, 2 or 3; t is equal to 0, 1, 2 or 3; q is an
 integer between 0 and 10,

20 and the optical and geometrical isomers of the said
 compounds of formula (I) as well as the salts thereof.

When the compounds according to the invention are in the form of salts, by addition of an acid, these are pharmaceutically or cosmetically acceptable salts obtained by addition of an inorganic or organic acid, 5 in particular hydrochloric acid, sulphuric acid, acetic acid, citric acid, fumaric acid, hemisuccinic acid, maleic acid or mandelic acid. When the compounds according to the invention are in the form of salts by addition of a base, these are salts of an alkali metal 10 or alkaline-earth metal or alternatively of zinc or of an organic amine.

According to the present invention, the term alkyl radical is understood to refer to a linear or branched radical optionally substituted with one or 15 more halogen atoms having from 1 to 20, preferably from 1 to 12, carbon atoms, advantageously methyl, ethyl, isopropyl, butyl, tert-butyl, hexyl, nonyl and dodecyl radicals. When it is lower, the alkyl radical generally comprises from 1 to 12 carbon atoms, preferably from 1 20 to 4 carbon atoms.

Among the linear alkyl radicals having from 1 to 20 carbon atoms, mention may be made in particular of the methyl, ethyl, propyl, 2-ethylhexyl, octyl, dodecyl, hexadecyl and octadecyl radicals.

25 Among the branched alkyl radicals having from 1 to 20 carbon atoms, mention may be made in particular of the 2-methylbutyl, 2-methylpentyl, 1-methylhexyl and 3-methylheptyl radicals.

Among the alkyl radicals having at least 4 carbon atoms, in which the carbon attached to the phenyl radical is substituted with at least two carbon atoms, mention may be made of the tert-butyl radical.

5 The term alkenyl radical is understood to refer to a linear or branched radical having from 1 to 20 carbon atoms and containing one or more double bonds.

10 Among the alkenyl radicals, a radical containing from 1 to 5 carbon atoms and having one or more ethylenic unsaturations, more particularly such as the allyl radical, is preferred.

15 The term alkynyl radical is understood to refer to a linear or branched radical having from 1 to 20 carbon atoms and containing one or more triple bonds.

Among the alkynyl radicals, a radical having from 2 to 6 carbon atoms, in particular a propargyl radical, is preferred.

20 The term lower acyl radical is understood to refer to a radical having from 1 to 6 carbon atoms and preferably the acetyl, propionyl and pivaloyl radicals.

25 The expression protecting group of an amine function is understood to refer to the corresponding groups described in "Protecting groups in organic synthesis" by T.W. Greene, Ed. by John Wiley and Sons (1981).

The term cycloalkyl radical is understood to

refer to a cyclic or polycyclic alkane radical containing from 1 to 10 carbon atoms, optionally substituted with one or more halogen atoms or one or more hydroxyl radicals, and preferably the adamantyl
5 and 1-methylcyclohexyl radicals.

The term polyether radical is understood to refer to a radical having from 1 to 6 carbon atoms and from 1 to 3 oxygen or sulphur atoms, such as the methoxymethyl ether, methoxyethoxymethyl ether or
10 methylthiomethyl ether radicals.

The expression monohydroxyalkyl or polyhydroxyalkyl radical should be understood to refer to a radical containing from 1 to 6 carbon atoms and from 1 to 5 hydroxyl groups.

15 Among the polyhydroxyalkyl radicals, a radical having from 3 to 6 carbon atoms and from 2 to 5 hydroxyl groups, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl radicals or the pentaerythritol residue, is preferred.

20 Among the optionally substituted aryl radicals, a phenyl radical optionally substituted with at least one halogen atom, a hydroxyl radical, an alkyl radical, a nitro function, a methoxy group or an optionally substituted amine function is preferred.

25 Among the optionally substituted aralkyl radicals, the benzyl or phenethyl radical optionally substituted with at least one halogen atom, a hydroxyl radical, a nitro function or a methoxy group is

preferred.

The term sugar residue is understood to refer to a residue derived in particular from glucose, galactose or mannose, or alternatively from glucuronic acid.

The term amino acid residue is understood to refer in particular to a residue derived from an amino acid such as lysine, glycine or aspartic acid, and the term peptide residue is understood to refer more particularly to a dipeptide or tripeptide residue resulting from the combination of amino acids.

The term heterocycle is understood to refer preferably to a piperidino, morpholino, pyrrolidino or piperazino radical, optionally substituted in position 4 with a C_1 - C_6 alkyl or polyhydroxyalkyl radical as defined above.

The term aminoalkyl radical is understood to refer to a radical preferably containing from 1 to 6 carbon atoms, in particular the aminomethyl, 3-aminopropyl and 6-aminoethyl radicals.

Among the cycloaliphatic radicals of C_3 to C_6 carbon atoms, mention may be made more particularly of the cyclopropyl and cyclohexyl radicals.

Among the halogen atoms, fluorine or chlorine is preferred.

When the radicals R_2 and R_3 represent a halogen atom, this is preferably a fluorine, bromine or chlorine atom.

Among the compounds of formula (I) above which fall within the scope of the present invention, mention may be made in particular of the following:

- 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylic acid,
- methyl 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylate,
- 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-5-carboxylic acid,
- methyl 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-5-carboxylate,
- 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid,
- methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate,
- 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid,
- methyl 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate,
- 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid,
- methyl 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-

benzofuran-5-carboxylate,

- 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid,

5 - methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylate,

- 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-10 6-carboxylic acid,

- methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-6-carboxylate,

15 - 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-5-carboxylic acid,

- methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-5-carboxylate,

20 - 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid,

- methyl 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-

25 carboxylate,

- [3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-oyl]morpholine,

- N-4-hydroxyphenyl-3-(5,6,7,8-tetrahydro-

- 5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxamide,
- N-butyl-3-methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-5-carboxamide,
- 5
- methyl 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylate,
 - 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylic acid,
- 10
- methyl 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate,
 - 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylic acid,
- 15
- methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylate,
 - 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylic acid,
- 20
- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-methanol,
 - 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carbaldehyde,
- 25
- methyl (-)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylate,

- methyl (+)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylate,
- methyl (-)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate,
- methyl (+)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate,
- methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylate,
- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylic acid,
- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-hexyl-2H-1-benzofuran-6-carboxylic acid,
- methyl 3-methoxycarbonylmethyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-6-carboxylate,
- 3-carboxymethyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-6-carboxylic acid.

According to the present invention, the compounds of formula (I) which are more particularly preferred are those for which at least one, and preferably all, of the conditions below are respected:

- R_1 is a radical $-(CH_2)_p-CO-O-R_{13}$

- R_2 is a hydrogen
- R_3 is a hydrogen or an alkenyl radical
- R_5 or R_6 is a radical $-OR_{11}$
- R_7 is a cycloalkyl radical
- 5 - Z_1 is an oxygen atom
- Y is a radical $C(R_9)_2$
- m is equal to 1.

The subject of the present invention is also processes for the preparation of the compounds of
10 formula (I), in particular according to the reaction schemes given in Figures 1 and 2.

Thus, the compounds of general formula (I) may be obtained (Figure 1) from the ketone II by halogenation, for example using a brominating agent
15 such as bromine. The compound III obtained is then coupled with the compound IV, in the presence of a base such as potassium carbonate or sodium hydride. The coupled derivative V is subjected to the action of a phosphine or a phosphonate in the presence of a base,
20 in order to lead to the compound VI. The compound VI is cyclized by the action of a metal catalyst such as palladium diacetate, in the presence of a hydride donor such as formic acid or of a nucleophile such as vinyltributyltin or lithium acetate and, if necessary,
25 a base.

The addition of silver zeolites or salts such as Ag_3PO_4 and of chiral phosphines such as binap makes it possible to induce an asymmetric cyclization.

The compounds of general formula (I) may thus be obtained according to the synthetic scheme of Figure 2. Compound VII is obtained by halogenation of the product IV with phosphorus pentachloride, for example.

5 It is converted into the phosphonium salt VIII by the action of triphenylphosphine (according to patent EP 428,423 A2). This is coupled with an aldehyde or a ketone IX, by the action of a base such as sodium methoxide or sodium hydride in order to give the enol
10 ether X. It is cyclized in the presence of a metal catalyst such as palladium diacetate, in the presence of a base such as tributylamine, in order to give the product XI. The compound of formula (I) is obtained after hydrogenation of the product XI.

15 The products of general formula (I) thus obtained may serve as starting materials for the manufacture of other products of general formula (I). These derivatives will be obtained according to the standard synthetic methods employed in chemistry, such
20 as those described in "Advanced Organic Chemistry" by J. March; John Wiley and Sons, 1985.

For example, functional modifications of the group R_1 may be carried out as indicated below:

carboxylic acid	→ ester
25 ester	→ carboxylic acid
acid	→ acid chloride
acid chloride	→ amide

	acid	→ amide
	acid	→ alcohol
	alcohol	→ aldehyde
	amide	→ amine
5	thiol	→ thioether
	thioether	→ sulphoxide
	thioether	→ sulphone
	sulphonic acid	→ sulphonic ester
	sulphonic acid	→ sulphonamide
10	sulphinic acid	→ sulphinic ester

The compounds according to the invention show activity in the test of differentiation of mouse embryonic teratocarcinoma cells (F9) (Cancer Research 43, pp. 5268, 1983) and/or in the test of inhibition of

15 ornithine decarboxylase after induction with TPA in mice (Cancer Research 38, pp. 793-801, 1978). These tests show the activities of these compounds in the fields of cell differentiation and cell proliferation respectively. In the test of cell (F9) differentiation,

20 an agonist activity may be evaluated as an antagonist activity to retinoic acid receptors. This is because an antagonist is inactive when it is alone in this test, but partially or totally inhibits the effect produced by a retinoid which is an agonist towards the

25 morphology and secretion of the plasminogen activator. Some of these compounds are thus also active in a test which consists in identifying the molecules which are

RAR antagonists, as described in French patent application No. 95/07302 filed on 19 June 1995 by the Applicant. This test comprises the following steps: (i) a sufficient amount of an RAR-agonist molecule is
5 applied topically to a part of the skin of a mammal, (ii) a molecule capable of exhibiting RAR-antagonist activity is administered systemically or topically to this same mammal or to this same part of the skin of the mammal, before, during or after step (i), and (iii)
10 the response on that part of the mammal's skin thus treated is evaluated. Thus, the response to a topical application, to the ear of a mammal, of an RAR-agonist molecule, which corresponds to an increase in the thickness of this ear, may be inhibited by the systemic
15 or topical administration of an RAR-antagonist molecule. In addition, some of these compounds may provide synergism to the biological activity of products binding to the nuclear receptors.

The subject of the present invention is also,
20 as medicinal product, the compounds of formula (I) as defined above.

The compounds according to the invention are particularly suitable in the following fields of treatment:

- 25 1) for treating dermatological complaints associated with a keratinization disorder which has a bearing on differentiation and on proliferation, in particular for treating common acne, comedones,

polymorphonuclear leukocytes, acne rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acnes such as solar acne, medication-induced acne or occupational acne,

- 5 2) for treating other types of keratinization disorders, in particular ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias and leucoplasiform states, and cutaneous or mucous (buccal) lichen,
- 10 3) for treating other dermatological complaints associated with a keratinization disorder having an inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis, whether it is cutaneous, mucous or ungual psoriasis, and even
15 psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema, or respiratory atopy or alternatively gingival hypertrophy; the compounds may also be used in certain inflammatory complaints which do not exhibit a disorder of keratinization,
- 20 4) for treating all dermal or epidermal proliferations, whether benign or malignant and whether or not they are of viral origin, such as common warts, flat warts and verruciform epidermodysplasia, it being also possible for the oral or florid papillomatoses and
25 the proliferations to be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular epithelioma,
- 5) for treating other dermatological disorders such

as bullosis and collagen diseases,

6) for treating certain ophthalmological disorders,
in particular corneopathies,

7) for repairing or combating both light-induced and
5 chronologically ageing of the skin or for reducing
actinic keratoses and pigmentations, or any pathology
associated with chronological or actinic ageing,

8) for preventing or curing the stigmata of epidermal
and/or dermal atrophy induced by local or systemic
10 corticosteroids, or any other form of skin atrophy,

9) for preventing or treating cicatrization disorders
or for preventing or repairing vibices,

10) for combating disorders of sebaceous functioning
such as the hyperseborrhoea of acne or simple
15 seborrhoea,

11) in the treatment or prevention of cancerous or
precancerous states,

12) in the treatment of inflammatory complaints such
as arthritis,

20 13) in the treatment of any complaint of viral origin
on the skin or generally, such as Kaposi's syndrome,

14) in the prevention or treatment of alopecia,

15) in the treatment of dermatological or general
complaints having an immunological component,

25 16) in the treatment of complaints of the
cardiovascular system such as arteriosclerosis,

17) in the treatment of skin disorders due to exposure
to UV radiation.

In the therapeutic fields mentioned above, the compounds according to the invention may advantageously be employed in combination with other compounds having retinoid-type activity, with D

5 vitamins or derivatives thereof, with corticosteroids, with anti-free-radical agents, α -hydroxy or α -keto acids or derivatives thereof, or alternatively with ion-channel blockers. The expression D vitamins or derivatives thereof is understood to refer, for

10 example, to vitamin D₂ or D₃ derivatives and in particular 1,25-dihydroxy vitamin D₃. The expression anti-free-radical agent is understood to refer, for example, to α -tocopherol, superoxide dismutase, ubiquinol or certain metal-chelating agents. The

15 expression α -hydroxy or α -keto acids or derivatives thereof is understood to refer, for example, to lactic acid, malic acid, citric acid, glycolic acid, mandelic acid, tartaric acid, glyceric acid or ascorbic acid or salts, amides or esters thereof. Lastly, the expression

20 ion-channel blockers is understood to refer, for example, to Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and derivatives thereof.

The subject of the present invention is also medicinal compositions containing at least one compound

25 of formula (I) as defined above, one of the optical or geometrical isomers thereof or one of the salts thereof.

The subject of the present invention is thus

a novel medicinal composition intended in particular for treating the abovementioned complaints, and which is characterized in that it comprises, in a pharmaceutically acceptable support which is compatible
5 with the mode of administration selected for this composition, at least one compound of formula (I), one of the optical or geometric isomers thereof or one of the salts thereof.

The compounds according to the invention may
10 be administered enterally, parenterally, topically or ocularly.

Via the enteral route, the medicinal products may be in the form of tablets, gelatin capsules, sugar-coated tablets, syrups, suspensions, solutions,
15 powders, granules, emulsions, microspheres or nanospheres or polymeric or lipid vesicles which allow controlled release. Via the parenteral route, the compositions may be in the form of solutions or suspensions for infusion or for injection.

20 The compounds according to the invention are generally administered at a daily dose of about 0.01 mg/kg to 100 mg/kg of body weight, taken in 1 to 3 doses.

Via the topical route, the pharmaceutical
25 compositions based on compounds according to the invention are more particularly intended for treating the skin and mucous membranes and may, in this case, be in the form of ointments, creams, milks, salves,

powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be in the form of microspheres or nanospheres or polymeric or lipid vesicles or polymeric patches and hydrogels which allow
5 controlled release. These topical-route compositions may moreover be either in anhydrous form or in an aqueous form, depending on the clinical indication.

Via the ocular route, they are mainly eyedrops.

10 These compositions for topical or ocular use contain at least one compound of formula (I) as defined above, or one of the optical or geometric isomers thereof, or alternatively one of the salts thereof, at
15 a concentration preferably of between 0.001% and 5% by weight relative to the total weight of the composition.

 The compounds of formula (I) according to the invention also find an application in the cosmetic field, in particular in body and hair hygiene and especially for treating skin-types with a tendency
20 towards acne, for promoting the regrowth of the hair, for combating hair loss, for controlling the greasy appearance of the skin or the hair, in protection against the harmful effects of sunlight or in the treatment of physiologically dry skin-types, and for
25 preventing and/or combating light-induced or chronological ageing.

 In the cosmetic field, the compounds according to the invention may also advantageously be

employed in combination with other compounds having retinoid-type activity, with D vitamins or derivatives thereof, with corticosteroids, with anti-free-radical agents, α -hydroxy or α -keto acids or derivatives thereof, or alternatively with ion-channel blockers, all of these different products being as defined above.

The present invention is thus also directed towards a cosmetic composition which is characterized in that it comprises, in a cosmetically acceptable support which is suitable for topical application, at least one compound of formula (I) as defined above, or one of the optical or geometric isomers thereof or one of the salts thereof, it being possible for this cosmetic composition to be, in particular, in the form of a cream, a milk, a lotion, a gel, microspheres or nanospheres or polymeric or lipid vesicles, a soap or a shampoo.

The concentration of compound of formula (I) in the cosmetic compositions according to the invention is advantageously between 0.001% and 3% by weight relative to the composition as a whole.

The medicinal and cosmetic compositions according to the invention may also contain inert additives or even pharmacodynamically or cosmetically active additives or combinations of these additives and, in particular, wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents such as

glycerol, PEG 400, thiamorpholinone and derivatives thereof, or, alternatively, urea; anti-seborrhoea or anti-acne agents such as S-carboxymethylcysteine, S-benzylcysteamine, the salts and the derivatives thereof, or benzoyl peroxide; antibiotics such as erythromycin and esters thereof, neomycin, clindamycin and esters thereof, and tetracyclines; antifungal agents such as ketoconazole or 4,5-polymethylene-3-isothiazolidones; agents for promoting the regrowth of the hair, such as Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and derivatives thereof, Diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and Phenytoin (5,4-diphenylimidazolidine-2,4-dione); non-steroidal anti-inflammatory agents; carotenoids and, in particular, β -carotene; anti-psoriatic agents such as anthraline and derivatives thereof and, lastly, eicosa-5,8,11,14-tetraynoic acid and eicosa-5,8,11-triynoic acid, the esters and the amides thereof.

The compositions according to the invention may also contain flavour-enhancing agents, preserving agents such as para-hydroxybenzoic acid esters, stabilizing agents, moisture regulators, pH regulators, osmotic pressure modifiers, emulsifying agents, UV-A and UV-B screening agents, and antioxidants such as α -tocopherol, butylhydroxyanisole or butylhydroxytoluene.

Several examples of the production of active

compounds of formula (I) according to the invention, as well as various solid formulations based on such compounds, will now be given by way of illustration and with no limitation. In the examples, TTN refers to
5 tetramethyltetrahydronaphthyl.

A. EXAMPLES OF COMPOUNDS

EXAMPLE 1

Process for the preparation of methyl 3-[3-(1-
adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-
10 carboxylate

4-Iodo-3-hydroxybenzoic acid.

3.6% sodium perchlorate solution is added dropwise to a mixture of 4-hydroxybenzoic acid (2.55 g, 18.5 mmol), sodium hydroxide (0.74 g, 18.5 mmol) and
15 sodium iodide (2.77 g, 18.5 mmol) in methanol (50 ml), at 0°C. The mixture is left stirring for two hours at 0°C. 20 ml of 10% sodium thiosulphate solution are added. After stirring, the mixture is acidified with hydrochloric acid to pH 1. It is extracted with 100 ml
20 of ethyl ether. The organic phase is washed twice with 80 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

White solid. Mass: 2.71 g. Yield: quantitative. m.p.:
25 178-185°C

¹H NMR (DMSO, 250 MHz): 7.13 (1H Ar, dd, J=1.08 Hz, J=7.55Hz), 7.41 (1H Ar, d, J=1.08 Hz), 7.76 (1H Ar, d, J=7.55 Hz), 10.71 (1H, s), 12.96 (1H, s).

Methyl 4-iodo-3-hydroxybenzoate.

A solution of 4-iodo-3-hydroxybenzoic acid (2.71 g, 10 mmol) and sulphuric acid (0.7 ml) in methanol (17 ml) is refluxed for 6 h. 20 ml of water are added and the mixture is basified with sodium bicarbonate until neutral. The mixture is extracted with ethyl ether (60 ml). The organic phase is washed with twice 30 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (50% ethyl acetate, 50% heptane).

White solid. Mass: 2 g. Yield: 72%. m.p.: 164°C

^1H NMR (CDCl_3 , 250 MHz): 3.91 (3H, s), 5.70 (1H, s), 7.33 (1H Ar, d, $J=8.16$ Hz), 7.64 (1H Ar, s), 7.75 (1H Ar, d, $J=8.16$ Hz).

Methyl 3-[(3-(1-adamantyl)-4-methoxybenzoyl)methyloxy]-4-iodobenzoate.

A solution of 3-(1-adamantyl)-4-methoxybromoacetophenone (2.5 g, 6.86 mmol), methyl 3-hydroxy-4-iodobenzoate (1.9 g, 6.83 mmol) and potassium carbonate (0.95 g, 6.88 mmol) in methyl ethyl ketone (50 ml) is refluxed for five hours. The reaction medium is filtered and 40 ml of water and 40 ml of ethyl ether are then added. After stirring and separation of the phases by settling, the organic phase is washed twice with 40 ml of water, dried over magnesium sulphate and concentrated on a rotary

evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (30% ethyl acetate, 70% heptane).

White solid. Mass: 2.52 g. Yield: 66%. m.p.: 156°C

5 ^1H NMR (CDCl_3 , 250 MHz): 1.77 (6H, s), 2.10 (9H, s), 3.88 (3H, s), 3.92 (3H, s), 5.37 (2H, s), 6.92 (1H Ar, d, $J=9.2$ Hz), 7.37 to 7.41, (2H Ar, m), 7.87 to 7.92 (3H Ar, m).

Methyl 4-iodo-3-[2-[3-(1-adamantyl)-4-methoxybenzyl]-1-propenyloxy]benzoate

10 Sodium methoxide (0.94 ml) is added over 8 hours to a mixture of methyl 3-[3-(1-adamantyl)-4-methoxybenzoylmethyloxy]-4-iodobenzoate (2.52 g, 4.49 mmol) and methyltriphenylphosphine bromide

15 (2.45 g) in THF (60 ml).

The mixture is stirred for 12 hours at room temperature. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. It is extracted with 40 ml of ethyl ether and 40 ml of water. After

20 separation of the phases by settling, the organic phase is washed twice with 40 ml of water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica

25 (60% CH_2Cl_2 , 40% heptane).

White solid. Mass: 1.16 g. Yield: 46%. m.p.: 73°C

^1H NMR (CDCl_3 , 250 MHz): 1.77 (6H, s), 2.06 (3H, s), 2.10 (6H, s), 3.85 (3H, s), 3.91 (3H, s), 4.98 (2H, s),

5.54 (2H, s), 6.86 (1H Ar, d, J=8.3 Hz), 7.28 to 7.40 (4H Ar, m), 7.51 (1H Ar, d, J=1.7 Hz), 7.86 (1H Ar, d, J=8.1 Hz).

Methyl 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-

5 1-benzofuran-6-carboxylate

A mixture of tributylamine (0.42 g, 2.26 mmol), triphenylphosphine (0.012 g, 0.05 mmol), palladium diacetate (0.005 g, 0.02 mmol) and methyl 4-iodo-3-[2-[3-(1-adamantyl)-4-methoxybenzyl]-1-propenyloxy]benzoate (1.13 g, 2.02 mmol) in 10 acetonitrile (12 ml) is heated at 95°C for 7 days. For the first 5 days, the reaction mixture is restocked with catalyst and triphenylphosphine. The reaction medium is concentrated on a rotary evaporator under 15 vacuum at 40°C.

20 ml of water and 20 ml of ethyl acetate are added. After separation of the phases by settling, the organic phase is washed twice with 20 ml of water, dried over magnesium sulphate and concentrated on a 20 rotary evaporator under vacuum at 40°C.

The product is purified by flash chromatography on a column of silica (50% CH₂Cl₂, 50% heptane).

White solid. Mass: 236 mg. Yield: 27%. m.p.: 91-92°C

25 ¹H NMR (CDCl₃, 250 MHz): 1.73 (9H, s), 2.03 (9H, s), 3.80 (3H, s), 3.90 (3H, s), 4.48 (1H, d, J=8.68 Hz), 4.61 (1H, d, J=8.68 Hz), 6.78 (1H Ar, d, J=8.52 Hz), 7.03 to 7.14 (3H Ar, m), 7.52 (1H Ar, d, J=1.14 Hz),

7.63 (1H Ar, dd, J=7.79 Hz, J=1.36 Hz).

^{13}C NMR (CDCl_3 , 250 MHz): 29.57, 29.24, 37.25, 37.37, 40.65, 49.86, 52.32, 55.21, 86.83, 111.02, 11.53, 123.12, 124.06, 124.79, 124.95, 130.69, 137.08, 138.69, 141.81, 157.72, 159.92, 167.22.

EXAMPLE 2

Process for the preparation of 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylic acid

10 A mixture of methyl 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylate (62 mg, 0.14 mmol), sodium hydroxide (0.012 g, 0.3 mmol) and lithium hydroxide (0.012 g, 0.28 mmol) is refluxed for 6 h. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of water and 10 ml of ethyl acetate are added. The mixture is acidified with concentrated hydrochloric acid solution to pH = 1. After separation of the phases by settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (50% CH_2Cl_2 50% EtOAc).

White solid. Mass: 43 mg. Yield: 72%. m.p.: 86°C

25 ^1H NMR (CDCl_3 , 250 MHz): 1.75 (9H, s), 2.03 (9H, s), 3.81 (3H, s), 4.50 (1H, d, J=8.68 Hz), 4.63 (1H, d, J=8.68 Hz), 6.79 (1H Ar, d, J=8.50), 7.05 (1H Ar, dd, J=2.27 Hz, J=8.48 Hz), 7.09 to 7.15 (2H Ar, m), 7.59

(1H Ar, s), 7.70 (1H Ar, dd, J=1.25 Hz, 7.79 Hz).

¹³C NMR (CDCl₃, 250 MHz): 25.95, 28.65, 36.66, 36.79, 40.07, 49.32, 54.63, 86.26, 110.95, 123.24, 123.59, 124.22, 124.34, 129.24, 136.35, 138.13, 142.27, 157.17.

5 EXAMPLE 3

Process for the preparation of methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate

Methyl 3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)methyloxy]-4-iodobenzoate.

A solution of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2'-bromoacetone naphthone (1.26 g, 4.1 mmol), methyl 3-hydroxy-4-iodobenzoate (1.15 g, 4.1 mmol) and potassium carbonate (0.62 g, 4.6 mmol) in methyl ethyl ketone (25 ml) is refluxed for three hours. The reaction medium is filtered and then concentrated on a rotary evaporator. 40 ml of water and 40 ml of ethyl acetate are added. After stirring and separation of the phases by settling, the organic phase is washed twice with 40 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (10% ethyl acetate, 90% heptane). White solid. Mass: 1.69 g. Yield: 81%. m.p.: 124°C

¹H NMR (CDCl₃, 250 MHz): 1.31 (6H, s), 1.32 (6H, s), 1.71 (4H, s), 3.88 (3H, s), 5.42 (2H, s), 7.35 to 7.41 (2H Ar, m), 7.43 (1H Ar, d, J=8.25 Hz), 7.74 (1H Ar, dd, J=8.25, J=2.5 Hz), 7.90 (1H Ar, d, J=7.5 Hz), 7.98

(1H Ar, d, J=2.5 Hz).

Methyl 4-iodo-3-[2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl]-1-propenyloxy]benzoate

Sodium methoxide (0.62 ml, 3.28 mmol) is
 5 added over 8 hours to a mixture of methyl 3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)methyloxy]-4-iodobenzoate (1.66 g, 3.28 mmol) and methyltriphenylphosphine bromide (1.63 g, 4.56 mmol) in THF (40 ml).

10 The mixture is stirred for two days at room temperature. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. It is extracted with 40 ml of ethyl ether and 40 ml of water. After separation of the phases by settling, the organic phase
 15 is washed twice with 40 ml of water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (60% CH₂Cl₂, 40% heptane).

20 White solid. Mass: 0.69 g. Yield: 42%. m.p.: 53°C
¹H NMR (CDCl₃, 250 MHz): 1.29 (6H, s), 1.30 (6H, s), 1.69 (4H, s), 3.91 (3H, s), 4.98 (2H, s), 5.58 (2H, s), 7.20 to 7.41 (4H Ar, m), 7.50 (1H Ar, d, J=1.15 Hz), 7.87 (1H Ar, d, J=8.00).
 25 ¹³C NMR (CDCl₃, 250 MHz): 31.34, 31.44, 33.71, 33.88, 34.55, 34.69, 51.86, 70.47, 92.84, 112.25, 113.66, 123.01, 123.06, 123.89, 131.08, 135.05, 139.12, 142.01, 144.53, 156.85, 166.05.

Methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate

A mixture of tributylamine (0.5 ml, 2.1 mmol), palladium diacetate (0.03 g, 0.2 mmol),
 5 formic acid (0.06 ml, 1.3 mmol) and methyl 4-iodo-3-[2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl]-1-propenyloxy]benzoate (0.65 g, 1.3 mmol) in acetonitrile (10 ml) is heated at 60°C for 4 h. The reaction medium is concentrated on a rotary evaporator under vacuum at
 10 40°C. 20 ml of water and 20 ml of ethyl ether are added. After separation of the phases by settling, the organic phase is washed twice with 20 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

15 The product is purified by flash chromatography on a column of silica (60% CH₂Cl₂, 40% heptane).

White solid. Mass: 330 mg. Yield: 68%. m.p.: 121°C

¹H NMR (CDCl₃, 250 MHz): 1.20 (3H, s), 1.22 (3H, s),
 20 1.25 (6H, s), 1.66 (4H, s), 1.73 (3H, s), 3.91 (3H, s), 4.48 (1H, d, J=8.75 Hz), 4.62 (1H, d, J=8.75 Hz), 7.00 (1H, dd, J=2 Hz, J=8.25 Hz), 7.09 (1H Ar, d, J=8 Hz), 7.18 to 7.24 (2 H Ar, m), 7.52 (1H Ar, s), 7.63 (1H Ar, d, J=8.00 Hz).

25 ¹³C NMR (CDCl₃, 250 MHz): 26.16, 31.77, 31.87, 33.96, 34.37, 35.01, 35.10, 49.79, 52.09, 86.48, 110.82, 122.84, 123.67, 123.93, 124.30, 126.60, 130.56, 141.35,

142.15, 143.32, 144.88, 159.80, 166.97.

EXAMPLE 4

Process for the preparation of 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-

5 benzofuran-6-carboxylic acid

A mixture of methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate (290 mg, 0.77 mmol), sodium hydroxide (0.06 g, 1.54 mmol) and lithium hydroxide
10 (0.06 g, 1.54 mmol) is stirred at room temperature for 24 h. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of water and 10 ml of ethyl acetate are added. The mixture is acidified with concentrated hydrochloric acid solution
15 to pH 1. After separation of the phases by settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is obtained by recrystallization from a heptane/ethyl
20 ether mixture (3/1).

White solid. Mass: 240 mg. Yield: 86%. m.p.: 206°C

¹H NMR (DMSO, 250 MHz): 1.17 (6H, s), 1.20 (6H, s),
1.61 (4H, s), 1.70 (3H, s), 4.50 (1H, d, J=9 Hz), 4.65
(1H, d, J=9 Hz), 6.98 (1H, d, J=8.25 Hz), 7.19 to 7.27
25 (3H Ar, m), 7.34 (1H Ar, s), 7.54 (1H Ar, d, J=7.75 Hz).

¹³C NMR (DMSO, 250 MHz): 25.81, 31.63, 31.73, 33.69,
34.09, 34.63, 34.71, 49.30, 85.43, 110.14, 122.62,

123.50, 123.79, 124.32, 126.56, 131.37, 140.89, 142.63,
142.72, 144.34, 159.37, 167.15.

EXAMPLE 5

Process for the preparation of methyl 3-methyl-3-

5 (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-
1-benzofuran-5-carboxylate

3-Iodo-4-hydroxybenzoic acid.

3.6% sodium perchlorate solution is added
dropwise to a mixture of 4-hydroxybenzoic acid
10 (12.75 g, 0.92 mol), sodium hydroxide (3.7 g, 0.92 mol)
and sodium iodide (13.85 g, 0.92 mol) in methanol
(350 ml) at 0°C. The mixture is left stirring for two
hours at 0°C. 100 ml of 10% sodium thiosulphate
solution are added. After stirring, the mixture is
15 acidified with hydrochloric acid to pH 1. It is
extracted with 600 ml of ethyl ether. The organic phase
is washed twice with 400 ml of water, dried over
magnesium sulphate and concentrated on a rotary
evaporator under vacuum at 40°C.

20 White solid. Mass: 28.76 g. Yield: quantitative.

m.p.: 157°C

¹H NMR (DMSO, 250 MHz): 6.74 (1H Ar, d, J=8.4 Hz), 7.71
(1H Ar, d, J=8.4 Hz), 8.13 (1H Ar, s), 10.16 (1H, s),
11.12 (1H, s).

25 Methyl 3-iodo-4-hydroxybenzoate.

A solution of 3-iodo-4-hydroxybenzoic acid
(28.76 g, 0.11 mol) and sulphuric acid (6.6 ml) in
methanol (160 ml) is refluxed for 6 h. 300 ml of water

are added and the mixture is basified with sodium bicarbonate until neutral. It is extracted with ethyl ether (600 ml). The organic phase is washed with twice 400 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on the column of silica (10% ethyl acetate, 90% CH₂Cl₂). White solid. Mass: 19.1 g. Yield: 63%. m.p.: 153°C

¹H NMR (CDCl₃, 250 MHz): 3.89 (3H, s), 7.01 (2H Ar, d, J=8.5 Hz), 7.94 (1H Ar, dd, J=8.5 Hz, J=2 Hz), 8.37 (1H Ar d, J=2 Hz)

Methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)methoxy]3-iodobenzoate.

A solution of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2'-bromoacetophenone (9.8 g, 0.032 mol), methyl 4-hydroxy-3-iodobenzoate (8.8 g, 0.032 mol) and potassium carbonate (8.5 g, 0.062 mol) in methyl ethyl ketone (450 ml) is refluxed for 1 day. The reaction medium is filtered and then concentrated on a rotary evaporator. 500 ml of water and 500 ml of ethyl ether are added. After stirring and separation of the phases by settling, the organic phase is washed twice with 500 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (10% ethyl acetate, 90% heptane). White solid. Mass: 9.56 g. Yield: 60%. m.p.: 125°C.

¹H NMR (CDCl₃, 250 MHz): 1.30 (6H, s), 1.32 (6H, s),

1.71 (4H, s), 3.88 (3H, s), 5.40 (2H, s), 6.70 (1H Ar, d, J=8.7 Hz), 7.43 (1H Ar, d, J=8.5 Hz), 7.74 (1H Ar, dd, J=2 Hz, J=8.5 Hz), 7.93 (1H Ar, dd, J=8.7, J=2.3 Hz), 7.98 (1H Ar, d, J=2 Hz), 8.48 (1H Ar, d, J=2.3 Hz).

Methyl 3-iodo-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate

30% sodium methoxide solution (2.67 g, 14.83 mmol) is added over 8 hours to a mixture of methyl 4-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)methoxy]-3-iodobenzoate (7.50 g, 14.8 mmol) and methyltriphenylphosphine bromide (7.30 g, 20.42 mmol) in THF (80 ml). The mixture is stirred for 18 hours at room temperature. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. This is extracted with 90 ml of ethyl ether and 90 ml of water. After separation of the phases by settling, the organic phase is washed twice with 90 ml of water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (70% CH₂Cl₂, 30% heptane). White solid. Mass: 4.71 g. Yield: 63%. m.p.: 126°C

¹H NMR (CDCl₃, 250 MHz): 1.29 (6H, s), 1.30 (6H, s), 1.69 (4H, s), 3.89 (3H, s), 4.99 (2H, s), 5.55 (1H, s), 5.59 (1H, s), 6.87 (1H Ar, d, J=8.7 Hz), 7.21 to 7.33 (2H Ar, m), 7.38 (1H Ar, d, J=1.8 Hz), 8.00 (1H Ar, dd, J=8.7, J=2 Hz), 8.48 (1H Ar, d, J=2 Hz).

^{13}C NMR (CDCl_3 , 250 MHz): 31.79, 31.90, 34.16, 34.33, 34.96, 35.10, 52.09, 70.81, 85.85, 111.35, 112.73, 114.05, 123.33, 124.17, 124.46, 126.71, 129.67, 131.45, 131.74, 135.23, 141.06, 141.99, 145.05, 145.10, 160.67, 165.47.

Methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylate

A mixture of tributylamine (2.28 ml, 9.6 mmol), palladium diacetate (0.06 g, 0.3 mmol), formic acid (0.29 ml, 7.4 mmol) and methyl 3-iodo-4-[2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl]-1-propenyloxy]benzoate (1.37 g, 2.72 mmol) in acetonitrile (25 ml) is heated at 95°C for 4 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C. 40 ml of water and 40 ml of ethyl ether are added. After separation of the phases by settling, the organic phase is washed twice with 20 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

The product is purified by flash chromatography on a column of silica, (50% CH_2Cl_2 , 50% heptane).

White solid. Mass: 630 mg. Yield: 61%. m.p.: 74°C

^1H NMR (CDCl_3 , 250 MHz): 1.20 to 1.24 (12H, m), 1.65 (4H, s), 1.73 (3H, s), 3.83 (3H, s), 4.51 (1H, d, $J=8.7$ Hz), 4.66 (1H, d, $J=8.7$ Hz), 6.87 (1H Ar, d, $J=8.3$ Hz), 6.96 (1H Ar, dd, $J=8.3$, $J=2$ Hz), 7.19 to 7.24 (2H Ar, m), 7.73 (1H Ar, d, $J=1.8$ Hz), 7.92 (1H

Ar, dd, J=8.3, J=2 Hz).

¹³C NMR (CDCl₃, 250 MHz): 26.63, 31.99, 32.08, 32.11,
34.18, 35.21, 35.32, 49.45, 52.04, 87.37, 109.82,
123.31, 123.98, 124.36, 126.46, 126.85, 131.41, 136.62,
5 142.56, 143.49, 145.04, 163.91, 167.19.

EXAMPLE 6

Process for the preparation of 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid

10 A mixture of methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylate (510 mg, 1.35 mmol), sodium hydroxide (0.33 g, 7.9 mmol), lithium hydroxide (0.33 g, 7.9 mmol) and water in THF is stirred at room
15 temperature for 5 days. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of water and 10 ml of ethyl acetate are added. The mixture is acidified with concentrated hydrochloric acid solution to pH 1. After separation of the phases by
20 settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The solid obtained is washed with heptane. White solid. Mass: 400 mg. Yield: 83%. m.p.: 246°C
25 ¹H NMR (DMSO, 250 MHz): 1.20 to 1.23 (12H, m), 1.64 (4H, s), 1.74 (3H, s), 3.83 (3H, s), 4.44 (1H, d, J=8.7 Hz), 4.66 (1H, d, J=8.7 Hz), 6.85 (1H Ar, d, J=7.5 Hz), 6.96 (1H Ar, dd, J=8.3, J=2 Hz), 7.19 to

7.24 (2H Ar, m), 7.73 (1H Ar, d, J=1.8 Hz), 7.92 (1H Ar, dd, J=8.3, J=2 Hz).

^{13}C NMR (DMSO, 250 MHz): 26.26, 31.63, 31.72, 31.75, 33.83, 34.25, 34.96, 35.06, 49.14, 87.01, 109.34, 123.36, 123.74, 124.03, 126.41, 126.52, 131.38, 136.25, 142.39, 143.02, 144.60, 163.59, 167.90.

EXAMPLE 7

Process for the preparation of methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-6-carboxylate
1,2,3,4-Tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran;
 (THTMDBF).

50 g (0.267 mmol) of bromoanisole dissolved in 120 ml of ethyl ether are treated at 0°C with 200 ml of n-butyllithium (1.6 M in hexane) and the medium is then left stirring at room temperature overnight. 41.57 g (273 mmol) of (+)-fenchone (Fluka) in 100 ml of ethyl ether are then added dropwise and the mixture is left stirring at room temperature for 6 h. The reaction medium is poured into 200 ml of saturated ammonium chloride solution.

After extraction with 600 ml of ethyl ether, rinsing with water, drying over magnesium sulphate, filtration and evaporation, the residue is chromatographed on silica to give 61.26 g (88%) of 2-O-anisyl-2-endofenchyl alcohol melting at 62-64°C; $\alpha_D = +78^\circ$ (c = 1, ethanol).

57.5 g (0.276 mmol) of phosphorus pentachloride are added at -10°C to a solution of 55.24 g (0.21 mmol) of 2-O-anisyl-2-endofenchyl alcohol and 4 g of calcium carbonate in 800 ml of chloroform.

5 The reaction mixture is stirred at room temperature for two hours, after which potassium carbonate (30 g) is added and the mixture is filtered. The solid residue is rinsed with chloroform and then chromatographed on silica in a hexane/ CH_2Cl_2 mixture
10 (9/1) to give 31.5 g (65%) of the expected derivative, melting at 68°C ; $\alpha_D = -39.5^{\circ}$ ($c = 1$, ethanol).

 The same synthesis carried out using (-)-fenchone leads to the dextrorotatory isomer of THTMDBF, melting at 68°C ; $\alpha_D = +36.3^{\circ}$ ($c = 1$, ethanol).

15 **1,2,3,4-Tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl methyl ketone**

 A solution containing 22.8 g (0.1 mmol) of (-)-THTMDBF and 7.8 ml (0.11 mmol) of acetyl chloride in 200 ml of dichloromethane is added dropwise to a
20 solution of 14.67 g of aluminium chloride (0.11 mmol) in 150 ml of CH_2Cl_2 . The reaction medium is left stirring for 4 h and is then poured into ice-water and extracted with CH_2Cl_2 . After the usual processing of the organic phase, followed by chromatography on silica in
25 a hexane/ethyl ether mixture (85/15), 17.26 g (64%) of the expected derivative, melting at $140-142^{\circ}\text{C}$, are isolated; $\alpha_D = -4.3^{\circ}$ ($c = 1$, ethanol).

1,2,3,4-Tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl bromomethyl ketone

18 g (66 mmol) of the ketone obtained in Example 3 in 100 ml of dioxane and 100 ml of ether are
5 treated by dropwise addition of a solution of 3.4 ml of bromine in 35 ml of CH_2Cl_2 . The reaction medium is left stirring for 2 hours at room temperature and is then poured into ice-water and extracted with 800 ml of ethyl ether. After drying and evaporation, the residue
10 is chromatographed on silica in a hexane/ CH_2Cl_2 mixture (50/50). 19.75 g (80%) of the expected derivative are obtained in the form of an orange-coloured oil.

Methyl 3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-oxymethoxy)-4-iodobenzoate

15 A solution of 1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl bromomethyl ketone (2.5 g, 6.86 mmol), methyl 3-hydroxy-4-iodobenzoate (1.9 g, 6.83 mmol) and potassium carbonate (0.95 g, 6.88 mmol) in methyl ethyl ketone (50 ml) is refluxed
20 for five hours. The reaction medium is filtered, after which 40 ml of water and 40 ml of ethyl ether are added. After stirring and separation of the phases by settling, the organic phase is washed twice with 40 ml of water, dried over magnesium sulphate and
25 concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (30% ethyl acetate, 70% heptane). Colourless oil. Mass: 3.2 g. Yield: 82%.

^1H NMR (CDCl_3 , 250 MHz): 0.85 to 1.67 (16H, m), 2.27 (1H, d, $J=3.75$ Hz), 3.88 (3H, s), 5.36 (2H, s), 6.79 (1H Ar, d, $J=8.5$ Hz), 7.38 to 7.40 (2H Ar, m), 7.71 (1H Ar, d, $J=1.75$ Hz), 7.86 to 7.90 (2H Ar, m).

5 Methyl 4-iodo-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-1-propenyloxybenzoate.

30% sodium methoxide solution in methanol (1 g, 5.56 mmol) is added dropwise over 8 h, under nitrogen and at room temperature, to a solution of
 10 methyl 3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-oyl)methyloxy)-4-iodobenzoate (3 g, 5.50 mmol) and methyltriphenylphosphine bromide (2.71 g, 7.58 mmol) in THF (30 ml).

The mixture is left stirring for 8 h at room
 15 temperature. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C . 50 ml of water and 50 ml of ethyl acetate are added. After separation of the phases by settling, the organic phase is washed twice with 50 ml of water, dried over magnesium
 20 sulphate and concentrated on a rotary evaporator under vacuum at 40°C . The product is purified by flash chromatography on a column of silica (90% CH_2Cl_2 , 10% heptane).

Colourless oil. Mass: 2.22 g. Yield: 74%.

25 ^1H NMR (CDCl_3 , 250 MHz): 0.87 to 1.66 (16H, m), 2.23 (1H, d, $J=3.75$ Hz), 3.91 (3H, s), 4.97 (2H, s), 5.51 (2H, s), 7.72 (1H Ar, d, $J=8.3$ Hz), 7.12 (1H Ar, s), 7.38 (1H Ar, d, $J=8.1$ Hz), 7.26 (1H Ar, dd, $J=1.6$ Hz),

7.51 (1H Ar, d, J=1.6 Hz, 7.86 (1H Ar, d, J=8.1 Hz).

¹³C NMR (CDCl₃, 250 MHz): 17.83, 19.44, 21.75, 23.44, 33.97, 42.12, 49.00, 50.72, 52.17, 55.56, 71.02, 93.15, 97.99, 108.59, 112.53, 112.95, 121.44, 123.31, 126.20, 129.97, 131.34, 133.83, 139.41, 142.18, 157.14, 158.75, 166.39

Methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-6-carboxylate.

10 A solution of methyl 4-iodo-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-1-propenyloxybenzoate (0.71 g, 1.3 mmol), palladium diacetate (0.03 g, 0.13 mmol), formic acid (0.06 ml, 1.6 mmol) and tributylamine (0.6 ml, 2.6 mmol) in 10 ml
15 of acetonitrile is heated at 80°C for 6 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C. 20 ml of water and 20 ml of ethyl ether are added. After separation of the phases by settling, the organic phase is washed twice with 20 ml of water,
20 dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. A mixture of the two diastereoisomers is obtained in a proportion of 50/50. The mixture of the two diastereoisomers is purified by flash chromatography on a column of silica
25 (80% CH₂Cl₂, 20% heptane).

Colourless oil. Mass: 465 mg. Yield: 85%.

¹H NMR (CDCl₃, 250 MHz): 0.76 to 1.63 (16H, m), 1.71 (3H, s), 2.21 (1H, d, J=4.3 Hz), 3.91 (3H, s), 4.48

- (1H, d, J=8.5 Hz), 4.58 (1H, d, J=8.5 Hz) and 4.56 (1H, d, J=8.5 Hz): 2 diastereoisomers, 6.65 (1H Ar, d, J=8.3 Hz, 6.84 (1H Ar, d, J=2 Hz) and 6.87 (1H Ar, d, J=2 Hz): 2 diastereoisomers, 6.99 to 7.05 (2H Ar, m), 7.51 (1H Ar, s), 7.62 (2H Ar, d, J=7.8 Hz).
- ¹³C NMR (CDCl₃, 250 MHz): 17.87 to 17.98: 2 diastereoisomers, 19.47, 21.92, 23.54, 26.49, 34.08 and 34.12: 2 diastereoisomers, 42.12 and 42.15: 2 diastereoisomers, 49.23, 49.57 and 49.65: 2 diastereoisomers, 50.87, 52.11, 55.73 and 55.76: 2 diastereoisomers, 86.82 and 86.86: 2 diastereoisomers, 97.93, 108.53 and 108.61: 2 diastereoisomers, 110.84, 121.41 and 121.65: 2 diastereoisomers, 122.92, 123.69 and 123.73: 2 diastereoisomers, 126.38 and 126.43: 2 diastereoisomers, 130.52, 134.05, 136.63 and 136.71: 2 diastereoisomers, 141.86 and 141.93: 2 diastereoisomers, 157.57, 159.66 and 159.70: 2 diastereoisomers, 166.98.

EXAMPLE 8

- Process for the preparation of 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)-2H-1-benzofuran-6-carboxylic acid

- A mixture of methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofuran-8-yl)-2H-1-benzofuran-6-carboxylate (0.41 g, 0.98 mmol), sodium hydroxide (0.1 g, 2.5 mmol), lithium hydroxide (0.1 g, 2.5 mmol), methanol and water in THF is stirred for 48 h at room temperature.

The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C, after which 10 ml of water are added. The suspension is acidified with concentrated hydrochloric acid solution to a pH of

- 5 1. The solid obtained is filtered off and is recrystallized from a heptane/ether mixture (1/5). White solid. Mass: 311 mg. Yield: 78%. m.p.: 184°C
- ^1H NMR (CDCl_3 , 250 MHz): 0.78 to 1.63 (16H, m), 1.73 (3H, s), 2.21 (1H, d, $J=3.8$ Hz), 4.51 (1H, d, $J=8.5$ Hz), 4.59 (1H, d, $J=8.5$ Hz) and 4.61 (1H, d, $J=8.5$ Hz): 2 diastereoisomers, 6.67 (1H Ar, d, $J=8.3$ Hz), 6.86 (1H Ar, d, $J=2$ Hz) and 6.89 (1H Ar, d, $J=2$ Hz): 2 diastereoisomers, 7.02 to 7.08 (2H Ar, m), 7.59 (1H Ar, s), 7.70 (2H Ar, d, $J=7.8$ Hz).
- 10 ^{13}C NMR (CDCl_3 , 250 MHz): 17.90 to 18.02: 2 diastereoisomers, 19.51, 21.94, 23.58, 26.48, 34.11, 42.15, 49.27, 49.65 and 49.73: 2 diastereoisomers, 50.91, 55.77, 86.88, 98.00, 108.61 and 108.70: 2 diastereoisomers, 111.40, 121.44 and 121.69: 2 diastereoisomers, 123.68 and 123.85: 2 diastereoisomers, 126.42 and 126.49: 2 diastereoisomers, 129.67, 134.14, 136.53 and 136.60: 2 diastereoisomers, 142.99 and 143.07: 2 diastereoisomers, 157.64, 159.74 and 159.78: 2 diastereoisomers, 171.94.
- 15
- 20
- 25

EXAMPLE 9

Process for the preparation of methyl 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate

A mixture of palladium bis(triphenylphosphine)diacetate (0.15 g, 0.2 mmol), tributylvinyltin (0.56 ml, 1.92 mmol) and methyl 4-iodo-3-[2-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl]-1-propenyloxy]benzoate (1 g, 1.99 mmol) in acetonitrile (20 ml) is heated at 80°C for 3 days, adding tributylvinyltin (0.28 ml, 0.96 mmol) every 24 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C. 40 ml of water and 40 ml of ethyl ether are added. After separation of the phases by settling, the organic phase is washed twice with 40 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

The product is purified by flash chromatography on a column of silica (80% CH₂Cl₂, 20% heptane).

Colourless oil. Mass: 250 mg. Yield: 32%.

¹H NMR (CDCl₃, 250 MHz): 1.13 (6H, s), 1.16 (6H, s), 1.57 (4H, s), 2.77 (2H, t, J=7 Hz), 3.79 (3H, s), 4.49 (1H, d, J=9 Hz), 4.55 (1H, d, J=9 Hz), 4.91 (1H, s), 4.97 (1H, d, J=6.5 Hz), 5.49 (1H, m), 6.92 (1H, dd, J=2 Hz, J=8.25 Hz), 7.05 (1H Ar, d, J=8.00 Hz), 7.07 to 7.14 (2H Ar, m), 7.41 (1H Ar, s), 7.54 (1H Ar, d, J=8.00 Hz).

¹³C NMR (CDCl₃, 250 MHz): 31.64, 31.76, 33.82, 34.24, 34.88, 34.97, 43.26, 51.93, 53.30, 83.69, 110.63, 118.78, 122.27, 123.84, 124.53, 124.82, 126.58, 130.58,

133.46, 138.42, 140.85, 143.21, 144.79, 160.24, 166.78.

EXAMPLE 10

Process for the preparation of 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-

5 benzofuran-6-carboxylic acid

A mixture of methyl 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate (240 mg, 0.61 mmol), sodium hydroxide (0.12 g, 3 mmol) and lithium hydroxide
10 (0.06 g, 3 mmol) is stirred at room temperature for 3 days. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of water and 10 ml of ethyl acetate are added. The mixture is acidified with concentrated hydrochloric acid solution
15 to pH 1. After separation of the phases by settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is obtained by recrystallization from a heptane/ethyl
20 ether mixture (3/1).

White solid. Mass: 128 mg. Yield: 54%, m.p.: 167°C

¹H NMR (CDCl₃, 250 MHz): 1.23 (6H, s), 1.26 (6H, s),
1.67 (4H, s), 2.89 (2H, t, J=7 Hz), 4.61 (1H, d,
J=8.75 Hz), 4.67 (1H, d, J=8.75 Hz), 5.04 (1H, s), 5.08
25 (1H, d, J=4.5 Hz), 5.60 (1H, m), 7.01 (1H, dd, J=2 Hz,
J=8.25 Hz), 7.17 to 7.22 (3H Ar, m), 7.57 (1H Ar, s),
7.71 (1H Ar, dd, J=1.3, J=8.00 Hz).

¹³C NMR (CDCl₃, 250 MHz): 32.05, 32.18, 34.27, 34.69,

35.29, 35.38, 43.63, 53.78, 84.18, 111.57, 119.31,
123.41, 124.26, 124.95, 125.37, 127.05, 130.05, 133.79,
139.97, 141.11, 143.74, 145.30, 160.69, 171.87.

EXAMPLE 11

5 Process for the preparation of [3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofur-5-oyl]-morpholine

A solution of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-
10 carboxylic acid (100 mg, 0.275 mmol), 1-hydroxybenzo-triazole (74 mg, 0.55 mmol) 1,3-dicyclohexyl-carbodiimide (112 mg, 0.55 mmol) and morpholine (0.024 ml, 0.255 mmol) in 5 ml of THF and 2 ml of DMF is stirred at room temperature for 6 hours. 30 ml of
15 water and 30 ml of ethyl acetate are added. After stirring and separation of the phases by settling, the aqueous phase is extracted with 2 x 30 ml of ethyl acetate. The organic phases are then combined and washed twice with 30 ml of water and then dried over
20 magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is then purified by flash chromatography on a column of silica (50% heptane/50% ethyl acetate).

White solid. Mass: 80 mg. Yield: 70%. m.p.: 57°C.

25 ¹H NMR (CDCl₃, 250 MHz): 1.18 (3H, s); 1.22 (3H, s); 1.26 (6H, s); 1.66 (4H, s); 1.73 (3H, s); 3.64 (8H, m); 4.52 (1H, d, J=9 Hz); 4.68 (1H, d, J=9 Hz); 6.87 (1H, d, J=8.25 Hz); 7.00 (1H, d, J=8.0 Hz); 7.11 to 7.29

(4H, m)

^{13}C NMR (CDCl_3 , 250 MHz): 26.03; 31.46; 31.57; 33.64;
34.03; 34.67; 34.77; 49.24; 66.56; 86.38; 109.37,
123.37; 123.64; 123.93; 126.30; 127.41; 128.05; 136.13;
5 142.01; 143.00; 144.48; 160.83; 170.37.

EXAMPLE 12

Process for the preparation of N-4-hydroxyphenyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxamide

10 A solution of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylic acid (100 mg, 0.275 mmol), 1-hydroxybenzotriazole (74 mg, 0.55 mmol), 1,3-dicyclohexylcarbodiimide (112 mg, 0.55 mmol) and 4-aminophenol (30 mg,
15 0.255 mmol) in 5 ml of THF and 2 ml of DMF is stirred at room temperature for 6 hours. 30 ml of water and 30 ml of ethyl acetate are added. After stirring and separation of the phases by settling, the aqueous phase is extracted with 2 x 30 ml of ethyl acetate. The
20 organic phases are then combined and washed twice with 30 ml of water and then dried over magnesium sulphate, and concentrated on a rotary evaporator under vacuum at 40°C. The product is then purified by flash chromatography on a column of silica (50% heptane/50%
25 ethyl acetate).

White solid. Mass: 45 mg. Yield: 36%. m.p.: 50°C.

^1H NMR (CDCl_3 , 250 MHz): 1.21 (3H, s); 1.25 (9H, s);
1.66 (4H, s); 1.74 (3H, s); 4.52 (1H, d, J=9 Hz); 4.68

(1H, d, J=9 Hz); 6.70 (2H, d, J=8.5 Hz); 6.90 (2H, d, J=8.5 Hz); 6.97 (1H, dd, J=8.75, 2.0); 7.20 to 7.27 (2H, m); 7.55 (1H, d, J=2.0 Hz); 7.72 (2H, m)

¹³C NMR (CDCl₃, 250 MHz): 26.2; 31.7; 31.9; 33.9; 34.3;

5 34.9; 35.0; 49.3; 87.0; 109.8; 115.9; 123.3; 123.6; 123.8; 126.7; 127.4; 128.4; 129.8; 136.7; 142.2; 143.3; 144.9; 153.7; 162.8; 166.2

EXAMPLE 13

Process for the preparation of N-butyl-3-methyl-3-

10 (5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-5-carboxamide

A solution of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylic acid (100 mg, 0.275 mmol), 1-hydroxybenzo-
15 triazole (74 mg, 0.55 mmol), 1,3-dicyclohexylcarbodiimide (112 mg, 0.55 mmol) and butylamine (19 mg, 0.255 mmol) in 5 ml of THF and 2 ml of DMF is stirred at room temperature for 6 hours. 30 ml of water and 30 ml of ethyl acetate are added. After stirring and
20 separation of the phases by settling, the aqueous phase is extracted with 2 x 30 ml of ethyl acetate. The organic phases are then combined and washed twice with 30 ml of water, then dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at
25 40°C. The product is then purified by flash chromatography on a column of silica (50% heptane/50% ethyl acetate).

Light oil. Mass: 80 mg. Yield: 69%.

¹H NMR (CDCl₃, 250 MHz): 0.93 (3H, t); 1.24 (3H, s);
 1.25 (6H, s); 1.36 (2H, m); 1.39 (2H, m); 1.62 (4H, s);
 1.78 (3H, s); 3.40 (2H, q, J=7.5 Hz, 13.0 Hz); 4.48
 (1H, d, J=9.0 Hz); 4.65 (1H, d, J=9.0 Hz); 6.65 (1H, d,
 5 J=8.4 Hz); 6.97 (1H, dd, J=8.75 Hz, 2.0 Hz); 7.22 (2H,
 m); 7.48 (1H, d, J=2.0 Hz); 7.62 (1H, dd, J=8.75 Hz,
 2.0 Hz)

¹³C NMR (CDCl₃, 250 MHz): 13.7; 20.1; 26.2; 31.68;
 31.74; 33.8; 34.3; 34.8; 34.9; 39.7; 49.3; 86.9; 109.4;
 10 123.4; 123.8; 124.0; 126.6; 127.7; 136.5; 142.3; 143.2;
 144.7; 162.2; 167.1

EXAMPLE 14

Process for the preparation of methyl 3-[4-(1-
adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-
 15 carboxylate
Methyl 3-[4-(1-adamantyl)-3-methoxybenzoylmethoxy]-4-
iodobenzoate

A solution of 4-(1-adamantyl)-3-methoxy-2'-
 bromoacetophenone (860 mg, 2.37 mmol), methyl
 20 3-hydroxy-4-iodobenzoate (660 mg, 2.37 mmol) and
 potassium carbonate (330 mg, 2.39 mmol) in methyl ethyl
 ketone (20 ml) is refluxed for five hours. The reaction
 medium is filtered and 30 ml of water and 30 ml of
 ethyl ether are then added. After stirring and
 25 separation of the phases by settling, the organic phase
 is washed twice with 30 ml of water, dried over
 magnesium sulphate and concentrated on a rotary
 evaporator under vacuum at 40°C. The product is

purified by flash chromatography on a column of silica (CH_2Cl_2).

White solid. Mass: 900 mg. Yield: 68%. m.p.: 136°C

^1H NMR (CDCl_3 , 250 MHz): 1.78 (6H, s), 2.11 (9H, s),
 5 3.89 (3H, s), 3.90 (3H, s), 5.42 (2H, s), 7.32 to 7.42
 (3H Ar, m), 7.43 (1H Ar, s, $J=1.5$ Hz), 7.48 (1H Ar, dd,
 $J=8$ Hz, $J=1.5$ Hz), 7.82 (1H Ar, d, $J=8$ Hz).

^{13}C NMR (CDCl_3 , 250 MHz): 28.97; 37.03; 37.76; 40.24;
 40.32; 52.42; 55.21; 71.62; 93.26; 110.35; 112.61;
 10 120.91; 124.15; 126.91; 131.65; 132.98; 139.94; 145.59;
 157.13; 159.34; 166.39; 192.69.

Methyl 4-iodo-3-[2-[4-(1-adamantyl)-3-methoxyphenyl]-1-propenyloxy]benzoate

A solution of 30% sodium methoxide in
 15 methanol (0.3 ml, 1.6 mmol) is added over 8 hours to a
 mixture of methyl 3-[4-(1-adamantyl)-3-methoxybenzoylmethyloxy]-4-iodobenzoate (870 mg,
 1.55 mmol) and methyltriphenylphosphine bromide (790
 mg, 2.21 mmol) in THF (10 ml).

20 The mixture is stirred at room temperature
 for 12 hours. The mixture is concentrated on a rotary
 evaporator under vacuum at 40°C . It is extracted with
 40 ml of ethyl ether and 40 ml of water. After
 separation of the phases by settling, the organic phase
 25 is washed twice with 40 ml of water, dried over
 anhydrous magnesium sulphate and concentrated on a
 rotary evaporator under vacuum at 40°C . The product is

purified by flash chromatography on a column of silica (60% CH₂Cl₂, 40% heptane).

White solid. Mass: 535 mg. Yield: 60%. m.p.: 109-111°C.

¹H NMR (CDCl₃, 250 MHz): 1.77 (6H, s); 2.09 (3H, s);

5 2.10 (6H, s); 3.86 (3H, s); 3.91 (3H, s); 4.98 (2H s);

5.62 (2H s); 7.00 to 7.04 (2H Ar, m); 7.21 (1H Ar, d,

J=7.25 Hz), 7.38 (1H Ar, dd, J=1.75 Hz, J=8.25 Hz),

7.50 (1H Ar, d, J=1.75 Hz), 7.87 (1H Ar, d, J=8 Hz).

¹³C NMR (CDCl₃, 250 MHz): 14.53; 23.11; 29.44; 29.51;

10 32.30; 37.35; 37.54; 41.00; 52.76; 55.55; 71.29; 93.70;

110.22; 113.12; 114.87; 118.66; 123.98; 126.97; 131.98;

137.35; 139.13; 140.03; 142.52; 157.69; 159.28; 166.93

Methyl 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylate

15 A mixture of tributylamine (0.44 ml, 1.84 mmol), sodium formate (70 mg, 1.01 mmol), palladium diacetate (20 mg, 0.092 mmol), 15-crown-5 (100 µl, 5 µmol) and methyl 4-iodo-3-[2-[4-(1-adamantyl)-3-methoxyphenyl]-1-prepenyloxy]benzoate (515
20 mg, 0.92 mmol) in acetonitrile (10 ml). Formic acid (0.035 ml, 0.92 mmol) is added after heating for 3 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C.

25 5 ml of water and 5 ml of ethyl acetate are added. After separation of the phases by settling, the organic phase is washed twice with 5 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

The product is purified by flash chromatography on a column of silica (70% CH₂Cl₂, 30% heptane).

White solid. Mass: 362 mg. Yield: 91%. m.p.: 108-111°C

5 ¹H NMR (CDCl₃, 250 MHz): 1.67 (9H, s), 1.98 (9H, s),
3.65 (3H, s), 3.83 (3H, s), 4.41 (1H, d, J=8.75 Hz),
4.57 (1H, d, J=8.75 Hz), 6.62 (1H Ar, d, J=1.75 Hz),
6.75 (1H Ar, dd, J=8.25 Hz, J=1.75 Hz), 7.02 (1H Ar, d,
J=7.75 Hz), 7.07 (1H Ar, d, J=7.75 Hz), 7.44 (1H Ar,
10 s), 7.55 (1H Ar, d, J=8 Hz).
¹³C NMR (CDCl₃, 250 MHz): 26.04, 29.10, 36.76, 37.15,
40.62, 49.79, 52.15, 54.98, 86.49, 110.17, 110.92,
118.24, 122.93, 123.96, 126.50, 130.72, 137.20, 141.20,
144.07, 158.88, 159.82, 166.97.

15 EXAMPLE 15

Process for the preparation of 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylic acid

A mixture of methyl 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylate
20 (320 mg, 0.74 mmol), sodium hydroxide (160 mg, 4 mmol), lithium hydroxide (160 mg, 4 mmol), methanol (1 ml) and water (1 ml) in THF (6 ml) is stirred at room temperature for 3 days. The mixture is concentrated on
25 a rotary evaporator under vacuum at 40°C. 10 ml of water and 10 ml of ethyl ether are added. The mixture is acidified with concentrated hydrochloric acid solution to pH = 1. After separation of the phases by

settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

- 5 White solid. Mass: 282 mg. Yield: 91%. m.p.: 217-222°C
- ¹H NMR (CDCl₃, 250 MHz): 1.76 (9H, s), 2.06 (9H, s), 3.74 (3H, s), 4.51 (1H, d, J=8.75 Hz), 4.67 (1H, d, J=8.75 Hz), 6.71 (1H Ar, s) 6.85 (1H Ar, d, J=8 Hz), 7.09 to 7.17 (2H Ar, m), 7.59 (1H Ar, s), 7.71 (1H Ar, d, J=7.75 Hz).
- 10 ¹³C NMR (CDCl₃, 250 MHz): 25.86, 28.85, 36.50, 36.92, 40.39, 49.54, 54.79, 86.16, 109.94, 110.88, 118.03, 122.92, 123.63, 126.24, 131.34, 136.85, 140.62, 143.99, 158.63, 159.52, 168.28.

15 **EXAMPLE 16**

Process for the preparation of methyl 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate

- 3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2'-
20 bromoacetone

- A solution of bromine (0.6 ml, 11.7 mmol) in dichloromethane (5 ml) is added dropwise to a solution of 3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-acetone (2.59 g, 10.6 mmol) in dioxane (15 ml) and ethyl ether (15 ml). The solution is stirred for 1 h at room temperature and is then poured on to a mixture of ice-water (25 g) and ethyl ether (25 ml). After separation of the phases by settling, the organic
- 25

phase is washed twice with water (25 ml), dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica

5 (50% CH₂Cl₂, 50% heptane) (Rf: 0.3).

White solid. Mass: 1.2 g. Yield: 35%. m.p.: oil

¹H NMR (CDCl₃, 250 MHz): 1.29 (6H, s), 1.30 (6H, s), 1.70 (4H, s), 2.49 (1H, s), 4.59 (3H, s), 7.18 (1H Ar, s), 7.67 (1H Ar, s).

10 Methyl 3-[(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)methyloxy]-4-iodobenzoate.

A solution of 3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2'-bromoacetophenone (1.20 g, 3.7 mmol), methyl 3-hydroxy-4-iodobenzoate (1.15 g, 4.1 mmol) and potassium carbonate (0.56 g, 4 mmol) in methyl ethyl ketone (25 ml) is refluxed for three hours. The reaction medium is filtered and then concentrated on a rotary evaporator. 40 ml of water and 40 ml of ethyl acetate are added. After stirring and separation of the phases by settling, the organic phase is washed twice with 40 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica

15
20
25 (80% CH₂Cl₂, 20% heptane), (Rf: 0.4).

White solid. Mass: 1.65 g. Yield: 86%. m.p.: 89-94°C

¹H NMR (CDCl₃, 250 MHz): 1.29 (6H, s), 1.31 (6H, s), 1.70 (4H, s), 2.49 (3H, s), 3.88 (3H, s), 5.30 (2H, s),

7.19 (1H Ar, s), 7.30 (1H Ar, s), 7.37 (1H Ar, d, J=8 Hz), 7.63 (1H Ar, s), 7.87 (1H Ar, d, J=8 Hz).

^{13}C NMR (CDCl_3 , 250 MHz): 20.94, 31.49, 31.87, 33.97, 34.46, 34.77, 34.83, 52.31, 72.54, 92.94, 112.36,

5 123.93, 126.99, 130.40, 131.49, 132.15, 139.83, 142.55, 149.94, 156.98, 166.27, 196.63.

Methyl 4-iodo-3-[2-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate

Sodium methoxide (0.62 ml, 3.17 mmol) is
10 added over 8 hours to a mixture of methyl 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl-methoxy)-4-iodobenzoate (1.6 g, 3.1 mmol) and methyltriphenylphosphine bromide (1.51 g, 4.2 mmol) in THF (15 ml).

15 The mixture is stirred for 3 days at room temperature. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. It is extracted with 30 ml of ethyl ether and 30 ml of water. After separation of the phases by settling, the organic phase
20 is washed twice with 30 ml of water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (90% CH_2Cl_2 , 10% heptane) (Rf: 0.67).

25 White solid. Mass: 0.54 g. Yield: 34%. m.p.: 83-86°C
 ^1H NMR (CDCl_3 , 250 MHz): 1.27 (6H, s), 1.29 (6H, s), 1.68 (4H, s), 2.32 (3H, s), 3.89 (3H, s), 4.76 (2H, s), 5.22 (1H, s), 5.77 (1H, s), 7.13 (1H Ar, d, J=6.75 Hz),

7.36 to 7.43 (2H Ar, m), 7.87 (1H Ar, d, $J=8.00$).

^{13}C NMR (CDCl_3 , 250 MHz): 31.91, 31.99, 33.97, 34.06, 35.22, 52.37, 71.51, 93.14, 112.58, 115.53, 123.50, 127.03, 128.26, 131.57, 132.49, 136.36, 139.62, 142.37, 143.71, 144.46, 157.19, 166.54.

Methyl 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate

A mixture of tributylamine (0.4 ml, 0.88 mmol), palladium diacetate (0.017 g, 0.083 mmol), formic acid (0.034 ml, 0.91 mmol), sodium formate (60 mg, 0.88 mmol), 15-crown-5 and methyl 4-iodo-3-[2-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate (429 mg, 0.83 mmol) in acetonitrile (10 ml) is heated at 45°C for 8 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C. 20 ml of water and 20 ml of ethyl ether are added. After separation of the phases by settling, the organic phase is washed twice with 20 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

The product is purified by flash chromatography on a column of silica (90% CH_2Cl_2 /10% heptane) (R_f : 0.38).

White solid. Mass: 180 mg. Yield: 55%. m.p.: 174.6°C
 ^1H NMR (CDCl_3 , 250 MHz): 1.21 (3H, s), 1.26 (9H, s), 1.67 (4H, s), 1.76 (3H, s), 1.97 (3H, s), 4.49 (1H, d,

$J=9$ Hz), 4.78 (1H, d, $J=9$ Hz), 7.03 to 7.05 (2H Ar, m), 7.28 (1H Ar, s), 7.48 (1H Ar, s), 7.61 (1H Ar, d, $J=7.75$ Hz).

^{13}C NMR (CDCl_3 , 250 MHz): 21.63; 29.52; 32.03; 32.13;

5 32.26; 32.38; 34.14; 34.48; 35.54; 35.61; 50.35; 52.51; 85.05; 110.95; 122.94; 124.27; 125.60; 130.87; 131.13; 133.71; 139.10; 142.00; 142.28; 144.06; 160.03; 167.44.

EXAMPLE 17

Process for the preparation of 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylic acid

A mixture of methyl 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate (140 mg, 0.36 mmol), sodium hydroxide (0.06 g, 1.54 mmol) and lithium hydroxide (0.06 g, 1.54 mmol) is stirred at room temperature for 24 h. The mixture is concentrated on a rotary evaporator under vacuum at 40°C. 10 ml of water and 10 ml of ethyl ether are added. The mixture is acidified with concentrated hydrochloric acid solution to pH 1. After separation of the phases by settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is obtained by recrystallization from a heptane/ethyl ether mixture (3/1). (90 EtOAc, 10 heptane) (R_f : 0.56). White solid. Mass: 118 mg. Yield: 87%. m.p.: 247°C

^1H NMR (CDCl_3 , 250 MHz): 1.20 (3H, s), 1.25 (9H, s),

1.66 (4H, s), 1.76 (3H, s), 1.98 (3H, s), 4.49 (1H, d, J=9 Hz), 4.77 (1H, d, J=9 Hz), 7.02 to 7.05 (2H Ar, m), 7.27 (1H Ar, s), 7.50 (1H Ar, s), 7.63 (1H Ar, d, J=7.15 Hz).

- 5 ^{13}C NMR (CDCl_3 , 250 MHz): 21.60; 29.48; 32.00; 32.10; 32.22; 32.35; 34.09; 34.43; 35.51; 35.57; 50.30; 84.94; 111.14; 123.16; 124.14; 125.57; 131.06; 131.56; 133.66; 139.17; 141.69; 142.20; 143.95; 159.92; 169.11.

EXAMPLE 18

- 10 Process for the preparation of methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylate
Tris[3,5-bis(1,1-dimethylethyl)-4-(trimethylsilyloxy)-phenyl]boroxine.

- 15 A 2.5 M solution of BuLi in hexane (4.7 ml, 11.8 mmol) is added dropwise to a suspension of 4-bromo-2,6-tert-butyl trimethylsilyloxyphenyl (4 g, 11.2 mmol) in TMEDA/THF (5 ml/40 ml) at -78°C . Stirring is continued for 1 h at the same temperature, after
- 20 which trimethyl borate is added dropwise at -78°C . Stirring is continued for 45 min at -78°C and 50 ml of saturated NH_4Cl solution are added. The mixture is allowed to return to room temperature. The pH of the solution is adjusted to 6.5 with concentrated HCl
- 25 solution. The mixture is extracted with CH_2Cl_2 , washed twice with water, dried and concentrated on a rotary evaporator under vacuum. The product is crystallized from heptane.

Yellow powder. Mass: 2.36 g. Yield: 66%. m.p. = 230°C
(235-237°C)¹²⁹

NMR δ ppm:

¹H (250 MHz, CDCl₃): 0.46 (9H, s), 1.47 (18H, s), 8.16
5 (2H, s).

Methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylate

A mixture of palladium diacetate (9 mg,
10 0.04 mmol), methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate (180 mg, 0.2 mmol), a solution containing 30% sodium methoxide in methanol (70 mg, 0.4 mmol) and the product tris[3,5-bis(1,1-dimethylethyl)-4-(trimethylsilyloxy)-
15 phenyl]boroxine (100 mg, 0.2 mmol) in DME (3 ml) is heated at 60°C for 2 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C and is treated with 10 ml of water and ethyl
20 ether. After separation of the phases by settling, the organic phase is washed twice with 10 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica (40% CH₂Cl₂, 60% heptane).

25 Amorphous yellow product. Mass: 22 mg. Yield: 19%.

NMR δ ppm:

¹H (250 MHz, CDCl₃): 1.20 to 1.27 (30H, m, CH₃ TTN and tBu), 1.67 (4H, s, CH₂ TTN), 3.10 (1H, d, J=13 Hz, H of

the CH₂ of the BHT), 3.40 (1H, d, J=13 Hz, H of the CH₂ of the BHT), 3.90 (3H, s, O-CH₃), 4.60 (1H, d, J=9 Hz, H of the O-CH₂), 4.92 (1H, d, J=9 Hz, H of the O-CH₂), 5.03 (1H, s, OH), 6.39 (2H Ar, s), 6.74 (1H Ar, d, J=8 Hz), 7.04 (1H Ar, dd, J=2 Hz, J=8.3 Hz), 7.23 to 7.27 (2H Ar, m), 7.42 (1H Ar, d, J=1.5 Hz), 7.54 (1H Ar, dd, J=1.5 Hz, J=8 Hz).

¹³C (250 MHz, CDCl₃): 30.19 (CH₃ tBu), 31.78 (CH₃ TTN), 31.86 (CH₃ TTN), 32.05 (CH₃ TTN), 33.96 (C tBu), 34.04 (C TTN), 34.39 (C TTN), 35.02 (CH₂ TTN), 35.10 (CH₂ TTN), 46.72 (CH₂), 52.10 (C), 55.39 (OCH₃), 83.49 (CH₂O), 111.77 (CH Ar), 121.53 (CH Ar), 124.32 (CH Ar), 124.96 (CH Ar), 126.51 (CH Ar), 126.60 (CH Ar), 126.94 (CH Ar), 127.08 (C Ar), 130.51 (C Ar), 134.86 (C Ar), 137.13 (C Ar), 140.47 (C Ar), 143.21 (C Ar), 145.02 (C Ar), 152.46 (C-O Ar), 160.53 (C-O Ar), 167.01 (COO).

EXAMPLE 19

Process for the preparation of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylic acid

A solution of the above product and sodium thiomethoxide (4 equivalents) in DMF is heated at 100°C for 4 h. Water and ethyl ether are added. The mixture is acidified to pH = 1 with concentrated hydrochloric acid solution. The organic phase is washed twice with water, dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.

White powder. Mass: 71 mg. Yield: 83%. m.p. = 211-213°C.

$C_{38}H_{48}O_4$ Mw: 568.80

Elemental analysis: Calculated: C: 80.24, H: 8.51.

5 Found: C: 80.00, H: 8.62.

MS m/z: 567 (M+).

IR (cm^{-1}): 1293 =C-O, 1436 C=C, 1688 C=O, 2959 C-H.

NMR δ ppm:

1H (250 MHz, $CDCl_3$): 1.21 to 1.27 (30H, m, CH_3 TTN and
10 tBu), 1.68 (4H, s, CH_2 TTN), 3.12 (1H, d, J=13 Hz, H of
the CH_2 of the BHT), 3.42 (1H, d, J=13 Hz, H of the CH_2
of the BHT), 4.61 (1H, d, J=9 Hz, H of the O- CH_2), 4.77
(1H, d, J=9 Hz, H of the O- CH_2), 5.01 (1H, s, OH), 6.39
(2H Ar, s), 6.76 (1H Ar, d, J=8 Hz), 7.06 (1H Ar, d,
15 J=8 Hz), 7.24 to 7.28 (2H Ar, m), 7.49 (1H Ar, s), 7.61
(1H Ar, d, J=8 Hz), 12.85 (1H, COOH).

^{13}C (250 MHz, $CDCl_3$): 30.24 (CH_3 tBu), 31.86 (CH_3 TTN),
31.92 (CH_3 TTN), 32.10 (CH_3 TTN), 34.02 (C tBu), 34.10
(C TTN), 34.46 (C TTN), 35.08 (CH_2 TTN), 35.16 (CH_2
20 TTN), 46.72 (CH_2), 55.52 (C), 83.57 (CH_2O), 111.33 (CH
Ar), 122.22 (CH Ar), 124.35 (CH Ar), 125.00 (CH Ar),
126.69 (CH Ar), 126.98 (CH Ar), 127.07 (C Ar), 129.55
(C Ar), 134.97 (C Ar), 138.27 (C Ar), 140.39 (C Ar),
143.34 (C Ar), 145.14 (C Ar), 152.55 (C-O Ar), 160.66
25 (C-O Ar), 171.08 (COO).

EXAMPLE 20

Process for the preparation of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzo-

furan-5-methanol

A 1M solution of borane in THF (7.7 ml, 7.7 mmol) is added dropwise at 0°C to a solution of 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid (1.7 g, 4.7 mol) in THF (10 ml). The mixture is stirred for 4 h at room temperature and 2 ml of a solution of THF and water (1:1) is then added. After concentration on a rotary evaporator under vacuum at 40°C. The mixture is extracted with ethyl acetate. The organic phase is washed with water, dried over anhydrous magnesium sulphate, concentrated on a rotary evaporator under vacuum at 40°C. The product is purified by flash chromatography on a column of silica.

Amorphous yellow solid. Mass: 1.7 g. Yield: quantitative.

$C_{24}H_{30}O_2$ Mw: 350.50

Calculated: C: 82.24, H: 8.63. Found: C: 82.40, H: 8.50.

MS m/z: 349 (M+).

NMR δ ppm:

1H (250 MHz, $CDCl_3$): 1.20 to 1.25 (12H, m), 1.66 (4H, s), 1.72 (3H, s), 3.47 (1H, s), 4.44 (1H, d, $J=8.8$ Hz), 4.59 (2H, s), 4.60 (1H, d, $J=8.8$ Hz), 6.84 (1H Ar, d, $J=8$ Hz), 7.01 (1H Ar, dd, $J=8.3$, $J=2.3$ Hz), 7.05 (1H Ar, d, $J=1.8$ Hz), 7.17 to 7.22 (3H Ar, m).
 ^{13}C (250 MHz, $CDCl_3$): 25.86 (CH_3), 31.39 (CH_3 TTN), 31.48 (CH_3 TTN), 31.51 (CH_3 TTN), 33.55 (C TTN), 33.97

(C TTN), 34.65 (CH₂ TTN), 34.75 (CH₂ TTN), 49.25 (C),
 65.05 (CH₂OH), 86.02 (CH₂O), 109.29 (CH Ar), 123.07 (CH
 Ar), 123.45 (CH Ar), 123.78 (CH Ar), 126.11 (CH Ar),
 127.26 (CH Ar), 133.18 (C Ar), 135.93 (C Ar), 142.38 (C
 5 Ar), 142.65 (C Ar), 144.27 (C Ar), 159.00 (C-O Ar).

EXAMPLE 21

Process for the preparation of 3-(5,6,7,8-tetrahydro- 5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzo- furan-5-carbaldehyde

10 A mixture of the alcohol obtained above (1 g,
 2.86 mmol) and pyridinium dichromate (2.15 g, 5.7 mmol)
 in dichloromethane is stirred at room temperature for
 3 h. After filtration and concentration on a rotary
 evaporator under vacuum at 40°C, the product is
 15 purified by flash chromatography on a column of silica.
 Oil. Mass: 0.98 g. Yield: 98%.

C₂₄H₂₈O₂ Mw: 348.48.

Elemental analysis: Calculated: C: 82.72, H: 8.10.

Found: C: 82.50, H: 8.10.

20 MS m/z: 349 (M+).

NMR δ ppm:

¹H (250 MHz, CDCl₃): 1.20 to 1.26 (12H, m), 1.67 (4H,
 s), 1.76 (3H, s), 4.57 (d, 1H, J=8.9), 4.73 (d, 1H,
 J=8.9), 6.96 (1H Ar, s), 7.00 (1H Ar, s), 7.20 to 7.25
 25 (2H Ar, m), 7.59 (1H Ar, d, J=1.5 Hz), 7.74 (1H Ar, dd,
 J=8.3 Hz, J=1.8 Hz), 9.83 (1H, s).

¹³C (250 MHz, CDCl₃): 26.44 (CH₃), 31.77 (CH₃ TTN),
 31.87 (CH₃ TTN), 31.91 (CH₃ TTN), 33.99 (C TTN), 34.39

(C TTN), 34.98 (CH₂ TTN), 35.09 (CH₂ TTN), 49.04 (C),
 87.45 (CH₂O), 110.26 (CH Ar), 123.74 (CH Ar), 124.12
 (CH Ar), 125.52 (CH Ar), 126.75 (CH Ar), 130.90 (C Ar),
 132.95 (CH Ar), 137.68 (C Ar), 141.99 (C Ar), 143.48 (C
 5 Ar), 144.94 (C Ar), 155.10 (C-O Ar), 190.67 (CHO).

EXAMPLE 22

Process for the preparation of methyl (-)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylate

10 A mixture of calcium carbonate (100 mg,
 1 mmol), palladium diacetate (10 mg, 0.05 mmol), sodium
 formate (68 mg, 1 mmol), methyl 3-iodo-4-[2-(5,6,7,8-
 tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyl-
 oxy]benzoate (250 mg, 0.5 mmol), (R)-(+)-2,2'-bis-
 15 (diphenylphosphino)-1,1'-binaphthyl (65 mg, 0.1 mmol)
 and silver zeolite (Aldrich 36,660-9) in acetonitrile
 (7 ml) is heated at 60°C for 2 days. The reaction
 medium is filtered through Celite and concentrated on a
 rotary evaporator under vacuum at 40°C. 10 ml of water
 20 and 10 ml of ethyl ether are added. After separation of
 the phases by settling, the organic phase is washed
 twice with 10 ml of water, dried over magnesium
 sulphate and concentrated on a rotary evaporator under
 vacuum at 40°C. The product is purified by flash
 25 chromatography on a column of silica.
 White solid. Mass: 105 mg. Yield: 56%. $[\alpha]_D^{20}$ (CHCl₃):
 -151°. ee: 68.4%.

EXAMPLE 23

Process for the preparation of methyl (+)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylate

Same procedure as above with (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

White solid. Mass: 75 mg. Yield: 40%. $[\alpha]_d^{20}$ (CHCl₃): +116°. ee: 58.8%.

EXAMPLE 24

Process for the preparation of methyl (-)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate

The experimental procedure is similar to that followed in order to obtain Example 22, applied to methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate.

White solid. Mass: 75 mg. Yield: 40%. $[\alpha]_d^{20}$ (CHCl₃): -29.8°. ee: 79.6%.

EXAMPLE 25

Process for the preparation of methyl (+)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate

The experimental procedure is similar to that followed in order to obtain Example 23, applied to methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate.

White solid. Mass: 75 mg. Yield: 40%. $[\alpha]_d^{20}$ (CHCl₃): +28.5°. ee: 81%.

EXAMPLE 26Process for the preparation of methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylate

- 5 Methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-octenyloxy]benzoate.

The experimental procedure is similar to that followed in order to obtain methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate, applied to methyl 3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)methyloxy]-4-iodobenzoate and hexyltriphenylphosphonium bromide.

White solid. Mass: 653 mg. Yield: 21%. m.p. = 62°C

- 15 $C_{30}H_{39}IO_3$ Mw = 574.54

Elemental analysis: Calculated: C: 62.72, H: 6.84.

Found: C: 62.41, H: 6.72.

MS m/z: 574 (M+)

IR (cm^{-1}): 1210 = C-O, 1490 C=C, 1718 C=O, 2956-2962

- 20 C-H.

NMR δ ppm:

- 1H (250 MHz, $CDCl_3$): 0.82 to 0.88 (twice 3H, m) 1.29 to 1.42 (18H, m, CH_3 TTN and CH_2 4.5 and 6), 1.67 (4H, s, CH_2 TTN), 2.03 (H No. 3 for the major product, d, J=7.5 Hz), 2.09 (H No. 3' for the major product, d, J=7.5 Hz), 2.28 (H No. 3 for the minor product, d, J=7.3 Hz), 2.33 (H No. 3' for the minor product, d, J=7.5 Hz), 3.89 (3H, s, for the major product), 3.91

- (3H, s, for the minor product), 4.78 (2H, s, for the major product), 4.96 (2H, s, for the minor product), 5.96 (1H, t, J=7.5 Hz, for the major product), 6.06 (1H, t, J=7.5 Hz, for the major product), 7.05 (1H Ar, d, J=8 Hz), 7.15 (1H Ar, s), 7.22 to 7.37 (2H Ar, m), 7.44 (1H Ar, s, for the major product), 7.52 (1H Ar, s, for the minor product), 7.83 (1H Ar, d, J=8).
- ¹³C (CDCl₃): 14.45 (CH₃), 22.63 (), 28.76 (), 29.58 (), 31.54 (), 31.65 (), 31.96 (CH₃ TTN), 31.99 (CH₃ TTN), 34.18 (C TTN), 34.31 (C TTN), 35.25 (CH₂ TTN), 52.36 (OCH₃), 73.83 (CH₂O), 93.51 (C-I), 112.98 (CH), 123.31 (CH), 125.77 (CH Ar), 126.36 (CH Ar), 127.19 (CH Ar), 131.48 (CH), 135.19 (C), 139.51 (CH), 143.74 (C), 144.59 (C), 157.45 (C-O Ar), 166.65 (COO).
- 15 Methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylate**
- A mixture of tributylamine (0.28 ml, 1.16 mmol), palladium diacetate (24 mg, 0.1 mmol) and methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-
- 20 tetramethyl-2-naphthyl)-2-octenyloxy]benzoate (610 mg, 1.06 mmol) in acetonitrile (15 ml) is heated at 80°C for 24 h. The reaction medium is concentrated on a rotary evaporator under vacuum at 40°C and then treated with 20 ml of water and ethyl ether. After separation**
- 25 of the phases by settling, the organic phase is washed twice with 20 ml of water, dried over magnesium sulphate and concentrated on a rotary evaporator under vacuum at 40°C.**

The product is purified by flash chromatography on a column of silica (80% CH₂Cl₂, 20% heptane).

Amorphous yellow. Mass: 305 mg. Yield: 64%.

5 C₃₀H₃₈O₃ Mw: 446.63

Elemental analysis:

Calculated: C: 80.68, H: 8.58. Found: C: 80.52, H: 8.38.

MS m/z: 446 (M+).

10 NMR δ ppm:

¹H (250 MHz, CDCl₃): 0.78 to 0.91 (twice CH₃ of the hexyl chains for the two products, m), 1.21 to 1.31 (16H, m, 4 CH₃ TTN and 1 CH₂), 1.55 to 1.73 (6H, m, 2 CH₂ TTN and 1 CH₂), 1.83 to 2.12 (2H, m, allylic CH₂),
15 3.90 (O-CH₃, s), 4.54-4.65 (CH₂O, m), 5.14 to 5.47 (2H ethylenic, m), 7.00 (twice 1H, d, J=8.12 Hz), 7.01 to 7.23 (twice 3H Ar, m), 7.47 (twice 1H Ar, m), 7.61 (twice 1H Ar, m).

EXAMPLE 27

20 Process for the preparation of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylic acid.

The experimental procedure is analogous to that followed in order to obtain Example 2, applied to
25 Example 26.

Yellow amorphous material. Mass: 285 mg, Yield: 80%.

C₂₉H₃₆O₃ Mw: 432.60

MS m/z: 431 (M+).

EXAMPLE 28Process for the preparation of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-hexyl-2H-1-benzofuran-6-carboxylic acid

- 5 A solution of the product of Example 27 in ethyl acetate, in the presence of palladium-on-charcoal at a pressure of 6 bar of hydrogen, is stirred at room temperature for 48 h. The mixture is filtered through Celite and then concentrated on a rotary evaporator
- 10 under vacuum at 40°C.

The product is purified by crystallization from CH₃CN.

White solid. Mass: 125 mg. Yield: 45%. m.p. = 137°C.

C₂₉H₃₈O₃ Mw: 434.62

- 15 Elemental analysis: Calculated: C: 80.14, H: 8.81, O: 11.04. Found: C: 79.72, H: 8.71, O: 10.67.

MS m/z: 433 (M+).

IR (cm⁻¹): 1292 = C-O, 1441 C=C, 1687 C=O, 2931-2963 C-H.

- 20 NMR δ ppm:

¹H (250 MHz, CDCl₃): 0.85 (3H, t, J=8.7 Hz), 1.20 to 1.26 (20H, m), 1.67 (4H, s), 2.09 (2H, t, J=7 Hz), 4.60 (2H, s), 7.00 (1H, d, J=8.3 Hz), 7.15 to 7.25 (3H Ar, m), 7.56 (1H Ar, s), 7.71 (1H Ar, d, J=7.8 Hz).

- 25 ¹³C (250 MHz, CDCl₃): 13.88 (CH₃), 22.47 (CH₂), 24.42 (CH₂), 29.63 (CH₂), 31.52 (CH₂), 31.66 (CH₃ TTN), 31.78 (CH₃ TTN), 33.85 (C TTN), 34.26 (C TTN), 34.93 (CH₂ TTN), 35.01 (CH₂ TTN), 38.87 (CH₂), 53.79 (C), 84.57

(CH₂O), 111.16 (CH Ar), 122.99 (CH Ar), 123.80 (CH Ar), 124.47 (CH Ar), 126.55 (CH Ar), 129.49 (C Ar), 140.25 (C Ar), 143.12 (C Ar), 144.78 (C Ar), 160.29 (C-O Ar), 171.64 (COO).

5 EXAMPLE 29

Process for the preparation of methyl 3-methoxy-carbonylmethyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-6-carboxylate

Methyl 4-iodo-3-[3-methoxycarbonyl-2-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)allyloxy]benzoate

The experimental procedure is similar to that followed in order to obtain methyl 4-iodo-3-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-1-propenyloxy]benzoate, applied to the product methyl 3-[(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthoyl)-methyloxy]-4-iodobenzoate and trimethyl phosphono-acetate.

White solid. Mass: 225 mg. Yield: 12%. m.p. = 115°C

C₂₇H₃₁IO₅ Mw: 561.9.

20 Elemental analysis: Calculated: C: 57.66, H: 5.56.

Found: C: 57.25, H: 5.68.

NMR δ ppm:

¹H (250 MHz, CDCl₃): 1.28 (6H, s, CH₃ TTN), 1.30 (6H, s, CH₃ TTN), 1.70 (4H, s, CH₂ TTN), 3.59 (3H, s, O-CH₃), 3.91 (3H, s, O-CH₃), 4.83 (2H, s), 6.50 (1H, s), 7.07 (1H Ar, d, J=8.2 Hz), 7.22 (1H Ar, s), 7.33 (1H Ar, d, J=8 Hz), 7.40 to 7.43 (2H Ar, m), 7.89 (1H Ar, d, J=8.2).

^{13}C (250 MHz, CDCl_3): 32.21 (CH_3 TTN), 34.59 (C TTN),
 34.66 (C TTN), 35.41 (CH_2 TTN), 51.61 (OCH_3), 52.71
 (OCH_3), 71.97 (CH_2O), 93.99 (C-I), 112.81 (CH), 117.30
 (CH), 124.28 (CH), 124.84 (CH), 126.70 (CH), 132.01
 5 (C), 133.32 (C), 140.07 (CH Ar), 145.09 (C), 145.76
 (C), 151.91 (C), 155.94 (C Ar), 166.65 (COO), 166.74
 (COO).

Methyl 3-methoxycarbonylmethyl-3-(5,5,8,8-tetramethyl-
 5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-
 10 6-carboxylate

The experimental procedure is similar to that
 followed in order to obtain Example 3, applied to the
 above product. The product is purified by flash
 chromatography on a column of silica (80% CH_2Cl_2 , 20%
 15 heptane).

Amorphous white product. Mass: 88 mg. Yield: 59%.

$\text{C}_{27}\text{H}_{32}\text{O}_5$ Mw: 436.55.

Elemental analysis: Calculated: C: 74.29, H: 7.39.

Found: C: 74.27, H: 7.28.

20 MS m/z: 436 (M+).

NMR δ ppm:

^1H (CDCl_3): 1.19 (6H, s, CH_3 TTN), 1.22 (6H, s, CH_3
 TTN), 1.64 (4H, s, CH_2 TTN), 3.03 (1H, d, J=15 Hz),
 3.31 (1H, d, J=15 Hz), 3.58 (3H, s, O- CH_3), 3.90 (3H,
 25 s, O- CH_3), 4.81 (1H, d, J=17 Hz), 4.92 (1H, d, J=17
 Hz), 6.96 (1H Ar, d, J=7.5 Hz), 7.14 to 7.21 (3H Ar,
 m), 7.50 (1H Ar, s), 7.60 (1H Ar, d, J=8.00 Hz).

^{13}C (CDCl_3): 32.06 (CH_3 TTN), 32.16 (CH_3 TTN), 32.20

(CH₃ TTN), 34.30 (C TTN), 34.72 (C TTN), 35.33 (CH₂ TTN), 35.40 (CH₂ TTN), 43.24 (CH₂), 52.00 (C), 52.08 (OCH₃), 52.48 (OCH₃), 84.55 (CH₂O), 111.40 (CH Ar), 122.98 (CH Ar), 123.59 (CH Ar), 123.98 (CH Ar), 124.97 (CH Ar), 127.27 (CH Ar), 131.42 (C Ar), 138.78 (C Ar), 140.75 (C Ar), 143.96 (C Ar), 145.35 (C Ar), 160.07 (C-O Ar), 167.19 (COO), 171.36 (COO).

EXAMPLE 30

Process for the preparation of 3-carboxymethyl-

10 3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphth-2-yl)-2H-1-benzofuran-6-carboxylic acid

The experimental procedure is similar to that followed in order to obtain Example 2, applied to the product of Example 29.

15 White powder. Mass: 51 mg. Yield: 71%. m.p. = 268°C.

C₂₅H₂₈O₅ Mw: 408.50

Elemental analysis: Calculated: C: 73.51, H: 6.91.

Found: C: 72.37, H: 6.88.

MS m/z: 407 (M+).

20 IR (cm⁻¹): 1258-1280 = C-O, 1411-1435 C=C, 1699 C=O, 2925 C-H.

NMR δ ppm:

¹H (DMSO): 1.19 (12H, s, CH₃ TTN), 1.21 (6H, s, CH₃ TTN), 1.52 (4H, s, CH₂ TTN), 3.06 (1H, d, J=16 Hz), 3.54 (1H, d, J=16 Hz), 4.83 (1H, d, J=10 Hz), 5.01 (1H, d, J=10 Hz), 7.04 (1H Ar, d, J=8.3 Hz), 7.21 (1H Ar, d, J=8.3 Hz), 7.29 to 7.31 (2H Ar, m), 7.36 (1H Ar, d, J=7.8 Hz), 7.47 (1H Ar, d, J=7.8 Hz).

^{13}C (DMSO): 31.52 (CH_3 TTN), 31.60 (CH_3 TTN), 33.61 (C TTN), 34.07 (C TTN), 34.61 (CH_2 TTN), 42.31 (CH_2), 50.63 (C), 83.44 (CH_2O), 110.06 (CH Ar), 122.28 (CH Ar), 122.86 (CH Ar), 123.13 (CH Ar), 124.59 (CH Ar), 126.57 (CH Ar), 131.40 (C Ar), 139.45 (C Ar), 141.45 (C Ar), 142.63 (C Ar), 144.31 (C Ar), 158.77 (C-O Ar), 167.03 (COO), 172.09 (COO).

B. FORMULATION EXAMPLES

1) ORAL ROUTE

10 (a) The following composition is prepared in the form of a 0.8 g tablet

	Compound of Example 1	0.005 g
	Pregelatinized starch	0.265 g
	Microcrystalline cellulose	0.300 g
15	Lactose	0.200 g
	Magnesium stearate	0.030 g

For the treatment of acne, 1 to 3 tablets are administered to an adult individual per day for 3 to 6 months, depending on the seriousness of the case

20 treated.

(b) A drinkable suspension intended to be packaged in 5 ml ampules is prepared

	Compound of Example 2	0.050 g
	Glycerol	0.500 g
25	70% sorbitol	0.500 g
	Sodium saccharinate	0.010 g
	Methyl para-hydroxybenzoate	0.040 g
	Flavouring qs	

Purified water qs 5 ml

For the treatment of acne, 1 ampule is administered to an adult individual per day for 3 months depending on the seriousness of the case

5 treated.

(c) The following formula intended to be packaged as gelatin capsules is prepared:

	Compound of Example 3	0.025 g
	Corn starch	0.060 g
10	Lactose qs	0.300 g

The gelatin capsules used consist of gelatin, titanium oxide and a preserving agent.

In the treatment of psoriasis, 1 gelatin capsule is administered to an adult individual per day
15 for 30 days.

2) TOPICAL ROUTE

(a) The following nonionic water-in-oil cream is prepared:

	Compound of Example 4	0.100 g
20	Mixture of emulsifying lanolin alcohols, refined oils and waxes, sold by the company BDF under the name "anhydrous eucerin"	39.900 g
	Methyl para-hydroxybenzoate	0.075 g
	Propyl para-hydroxybenzoate	0.075 g
25	Sterile demineralized water qs	100.000 g

This cream is applied to psoriatic skin 1 to 2 times a day for 30 days.

(b) A gel is prepared by producing the following

formulation:

	Compound of Example 5	0.050 g
	Erythromycin base	4.000 g
	Butylhydroxytoluene	0.050 g
5	Hydroxypropylcellulose sold by the company Hercules under the name "Klucel HF"	2.000 g
	Ethanol (95°) qs	100.000 g

This gel is applied to skin attacked by
10 dermatitis or to acneic skin 1 to 3 times a day for 6
to 12 weeks depending on the seriousness of the case
treated.

(c) An anti-seborrhoea lotion is prepared by mixing
together the following ingredients:

15	Compound of Example 6	0.030 g
	Propylene glycol	5.000 g
	Butylhydroxytoluene	0.100 g
	Ethanol (95°) qs	100.000 g

This lotion is applied twice a day to a
20 seborrhoeic scalp and a significant improvement is
observed within 2 to 6 weeks.

(d) A cosmetic composition to combat the harmful
effects of sunlight is prepared by mixing together the
following ingredients:

25	Compound of Example 7	1.000 g
	Benzylidenecamphor	4.000 g
	Fatty acid triglycerides	31.000 g
	Glyceryl monostearate	6.000 g

	Stearic acid	2.000 g
	Cetyl alcohol	1.200 g
	Lanolin	4.000 g
	Preserving agents	0.300 g
5	Propylene glycol	2.000 g
	Triethanolamine	0.500 g
	Fragrance	0.400 g
	Demineralized water qs	100.000 g

This composition is applied daily and makes
 10 it possible to combat light-induced ageing.

(e) The following nonionic oil-in-water cream is
 prepared:

	Compound of Example 8	0.500 g
	Vitamin D3	0.020 g
15	Cetyl alcohol	4.000 g
	Glyceryl monostearate	2.500 g
	PEG-50 stearate	2.500 g
	Karite butter	9.200 g
	Propylene glycol	2.000 g
20	Methyl para-hydroxybenzoate	0.075 g
	Propyl para-hydroxybenzoate	0.075 g
	Sterile demineralized water qs	100.000 g

This cream is applied to psoriatic skin 1 to
 2 times a day for 30 days.

25 (f) A topical gel is prepared by mixing together the
 following ingredients:

	Compound of Example 9	0.050 g
	Ethanol	43.000 g

	α -Tocopherol	0.050 g
	Carboxyvinyl polymer sold under the name Carbopol 941" by the company "Goodrich"	0.500 g
5	Triethanolamine as an aqueous 20% by weight solution	3.800 g
	Water	9.300 g
	Propylene glycol qs	100.000 g

This gel is applied in the treatment of acne
10 1 to 3 times a day for 6 to 12 weeks depending on the
seriousness of the case treated.

(g) A lotion to prevent hair loss and promote regrowth
of the hair is prepared by mixing together the
following ingredients:

15	Compound of Example 10	0.05 g
	Compound sold under the name "Minoxidil"	1.00 g
	Propylene glycol	20.00 g
	Ethanol	34.92 g
20	Polyethylene glycol (molecular mass = 400)	40.00 g
	Butylhydroxyanisole	0.01 g
	Butylhydroxytoluene	0.02 g
	Water qs	100.00 g

25 This lotion is applied twice a day for 3
months to a scalp which has lost a considerable amount
of hair.

(h) An anti-acne cream is prepared by mixing together

the following ingredients:

	Compound of Example 6	0.050 g
	Retinoic acid	0.010 g
	Mixture of glyceryl stearate and	
5	polyethylene glycol stearate (75 mol)	
	sold under the name "Gelot 64" by the	
	company "Gattefosse"	15.000 g
	Core oil polyoxyethylenated with 6 mol	
	of ethylene oxide, sold under the	
10	name "Labrafil M2130 CS" by the	
	company "Gattefosse"	8.000 g
	Perhydrosqualene	10.000 g
	Preserving agents	qs
	Polyethylene glycol (molecular	
15	mass = 400)	8.000 g
	Disodium salt of ethylenediamine-	
	tetraacetic acid	0.050 g
	Purified water qs	100.000 g

This cream is applied to skin attacked by
 20 dermatitis or to acneic skin 1 to 3 times a day for 6
 to 12 weeks.

(i) An oil-in-water cream is prepared by producing the
 following formulation:

	Compound of Example 5	0.020 g
25	Betamethasone 17-valerate	0.050 g
	S-Carboxymethylcysteine	3.000 g
	Polyoxyethylene stearate (40 mol of	
	ethylene oxide) sold under the name	

	"Myrj 52" by the company "Atlas"	4.000 g
	Sorbitan monolaurate, polyoxyethylenated with 20 mol of ethylene oxide, sold under the name "Tween 20" by the	
5	company "Atlas"	1.800 g
	Mixture of glyceryl monostearate and glyceryl distearate, sold under the name "Géléol" by the company	
	"Gattefosse"	4.200 g
10	Propylene glycol	10.000 g
	Butylhydroxyanisole	0.010 g
	Butylhydroxytoluene	0.020 g
	Cetostearyl alcohol	6.200 g
	Preserving agents	qs
15	Perhydrosqualene	18.000 g
	Mixture of caprylic/capric triglycerides sold under the name "Miglyol 812" by the company	
	"Dynamit Nobel"	4.000 g
20	Triethanolamine (99% by weight)	2.500 g
	Water qs	100.000 g

This cream is applied twice a day to skin
attacked by dermatitis, for 30 days.

(j) The following cream of oil-in-water type is

25 prepared:

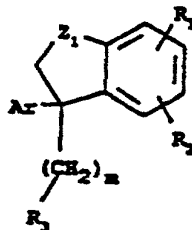
Lactic acid	5.000 g
Compound of Example 2	0.020 g
Polyoxyethylene stearate (40 mol of	

	ethylene oxide) sold under the name	
	"Myrj 52" by the company "Atlas"	4.000 g
	Sorbitan monolaurate, polyoxy-	
	ethylenated with 20 mol of ethylene	
5	oxide, sold under the name "Tween 20"	
	by the company "Atlas"	1.800 g
	Mixture of glyceryl monostearate and	
	glyceryl distearate, sold under the	
	name "Geleol" by the company	
10	"Gattefosse"	4.200 g
	Propylene glycol	10.000 g
	Butylhydroxyanisole	0.010 g
	Butylhydroxytoluene	0.020 g
	Cetostearyl alcohol	6.200 g
15	Preserving agents	qs
	Perhydrosqualene	18.000 g
	Mixture of caprylic/capric	
	triglycerides sold under the name	
	"Miglyol 812" by the company	
20	"Dynamit Nobel"	4.000 g
	Water qs	100.000 g

This cream is applied once a day and helps to combat both light-induced and chronological ageing.

CLAIMS

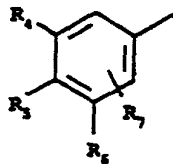
1. Heterocyclic biaryl compounds,
characterized in that they correspond to the general
formula (I) below:



(I)

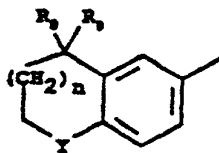
5 in which:

- Ar represents
- . either the radical of formula (II) below:



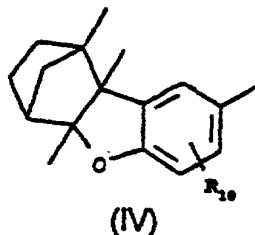
(II)

- . or the radical of formula (III) below:



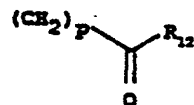
(III)

- . or the radical of formula (IV) below:



- R_1 represents an atom or a radical chosen from

- (i) the $-\text{CH}_3$ radical,
- (ii) the radical $-(\text{CH}_2)_p-\text{O}-R_{11}$,
- (iii) a radical $-\text{OR}_{11}$,
- (iv) a radical



- (v) a radical $-\text{S}(\text{O})_t R_{13}$,

R_{11} , R_{12} , R_{13} , p and t having the meanings given below,

- R_2 represents a hydrogen atom, a halogen atom, an alkyl radical or the radical $-\text{OR}_{11}$,

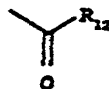
R_{11} having the meaning given below,

- R_3 represents an atom or a radical chosen from:

- (i) an atom or a radical chosen from a hydrogen atom, an alkyl radical, an alkenyl radical, an alkynyl radical, an aryl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical, a cyano radical or a radical $-\text{O}-R_{11}$,

R_{11} having the meaning given below,

- (ii) a radical



R_{12} having the meaning given below,

(iii) a radical



r and r' having the meaning given below,

- Z_1 represents O, S or NR' ,

5 - m is an integer between 0 and 10,

it being understood in all of the preceding text that:

R_4 , R_5 , R_6 and R_7 , which may be identical or different, are chosen from:

(i) a hydrogen atom,

10 (ii) an alkyl radical having at least 4 carbon atoms, among which the carbon attached to the phenyl radical is substituted with at least two carbon atoms,

(iii) a cycloalkyl radical,

15 (iv) a radical $-(\text{Z}_2)_n-(\text{CH}_2)_q-\text{CO}-\text{R}_{12}$,

(v) a radical $-\text{Z}_3-\text{R}_{11}$,

with at least one of the radicals R_4 , R_5 , R_6 and R_7 being an alkyl radical as defined in (ii) or a cycloalkyl radical (iii),

20 Z_2 , Z_3 , R_{11} , R_{12} , n and q having the meanings given below,

R_8 and R_9 represent lower alkyl radicals,

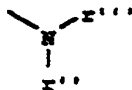
R_{10} represents a lower alkyl radical, a radical $-OR_{11}$ or a polyether radical,

R_{11} , which may be identical or different, represents a
 5 hydrogen atom, a lower alkyl radical, an aryl radical, an aralkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, a polyether radical or a lower acyl radical,

R_{12} , which may be identical or different, represents:

10

- (a) a hydrogen atom, an alkynyl radical, an alkenyl radical, an alkyl radical or a heterocycle,
- (b) a radical



15

r'' and r''' having the meaning given below

- (c) a radical $-OR_{13}$

R_{13} , which may be identical or different, represents a
 hydrogen atom, an alkyl radical, a monohydroxyalkyl or polyhydroxyalkyl radical, an optionally substituted
 20 aryl or aralkyl radical or a sugar, amino acid or peptide residue,

R', which may be identical or different, represents a protecting group for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical or an optionally substituted aryl radical or an amino acid, peptide or sugar residue,

r and r', which may be identical or different, represent protecting groups for amine functions, a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

r'' and r''', which may be identical or different, represent a hydrogen atom, a lower alkyl radical, a polyether radical, an optionally substituted aryl radical or an amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

Y represents $C(R_9)_2$, O, S, Nr' , CHOH, CO, SO or SO_2 ,

Z_2 represents O, S or NR' ,

Z_3 represents O or S,

n, which may be identical or different, is equal to 0 or 1; p, which may be identical or different, is equal to 0, 1, 2 or 3; t is equal to 0, 1, 2 or 3; q is an

integer between 0 and 10,
as well as the salts thereof and the optical and
geometrical isomers thereof.

2. Compounds according to Claim 1,
5 characterized in that they are in the form of salts of
an alkali metal or alkaline-earth metal, of zinc, of an
organic amine or of an inorganic or organic acid.

3. Compounds according to either of Claims
1 and 2, characterized in that the alkyl radicals are
10 chosen from the group consisting of the methyl, ethyl,
isopropyl, butyl, tert-butyl, hexyl, nonyl and dodecyl
radicals.

4. Compounds according to one of the
preceding claims, characterized in that
15 polyhydroxyalkyl radicals are chosen from the group
consisting of the 2,3-dihydroxypropyl, 2,3,4-
trihydroxybutyl and 2,3,4,5-tetrahydroxypentyl radicals
or the pentaerythritol residue.

5. Compounds according to one of the
20 preceding claims, characterized in that the aryl
radical is a phenyl radical optionally substituted with
at least one halogen atom, a hydroxyl radical, an alkyl
radical, a nitro function, a methoxy group or an
optionally substituted amine function.

25 6. Compounds according to one of the
preceding claims, characterized in that the aralkyl
radicals are chosen from the group consisting of the
benzyl and phenethyl radicals, optionally substituted

with at least one halogen atom, a hydroxyl, a nitro function or a methoxy group.

7. Compounds according to one of the preceding claims, characterized in that the alkenyl radicals are chosen from the group consisting of radicals containing from 1 to 5 carbon atoms and having one or more ethylenical unsaturations, and in particular the allyl radical.

8. Compounds according to one of the preceding claims, characterized in that the sugar residues are chosen from the group consisting of glucose, galactose, mannose and glucuronic acid residues.

9. Compounds according to any one of the preceding claims, characterized in that the amino acid residues are chosen from the group consisting of residues derived from lysine, from glycine or from aspartic acid.

10. Compounds according to any one of the preceding claims, characterized in that the peptide residues are chosen from the group consisting of dipeptide and tripeptide residues.

11. Compounds according to any one of the preceding claims, characterized in that the heterocyclic radicals are chosen from the group consisting of piperidino, morpholino, pyrrolidino and piperazino radicals, optionally substituted in position 4 with a C_1 - C_6 alkyl or a polyhydroxyalkyl radical.

12. Compounds according to any one of the preceding claims, characterized in that the halogen atoms are chosen from the group consisting of fluorine and chlorine.

5 13. Compounds according to any one of the preceding claims, characterized in that the aminoalkyl radical is chosen from the aminomethyl, 3-aminopropyl and 6-aminohexyl radicals.

10 14. Compounds according to any one of the preceding claims, characterized in that the alkynyl radical has from 2 to 6 carbon atoms.

15 15. Compounds according to any one of the preceding claims, characterized in that the cycloaliphatic radicals of C3 to C6 carbon atoms are chosen from the cyclopropyl radical and the cyclohexyl radical.

20 16. Compounds according to any one of the preceding claims, characterized in that the lower acyl radicals are chosen from the acetyl, propionyl and pivaloyl radicals.

17. Compounds according to any one of the preceding claims, characterized in that the cycloalkyl radicals are chosen from the adamantyl and 1-methyl-cyclohexyl radicals.

25 18. Compounds according to any one of the preceding claims, characterized in that the polyether radicals are chosen from the methoxymethyl ether, methoxyethoxymethyl ether and methylthiomethyl ether

radicals.

19. Compounds according to Claim 1, characterized in that they are taken, alone or as mixtures, from the group consisting of:

- 5 - 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylic acid,
 - methyl 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-6-carboxylate,
 - 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-5-carboxylic acid,
10 - methyl 3-[3-(1-adamantyl)-4-methoxyphenyl]-3-methyl-2H-1-benzofuran-5-carboxylate,
 - 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic
15 acid,
 - methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate,
 - 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-
20 carboxylic acid,
 - methyl 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate,
 - 3-(propen-2-yl)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-
25 carboxylic acid,
 - methyl 3-(propen-2-yl)-3-(5,6,7,8-

- tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylate,
- 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylic acid,
 - methyl 3-methyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-5-carboxylate,
 - 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-6-carboxylic acid,
 - methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-6-carboxylate,
 - 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-5-carboxylic acid,
 - methyl 3-methyl-3-(1,2,3,4-tetrahydro-1,4a,9b-trimethyl-1,4-methanodibenzofur-8-yl)-2H-1-benzofuran-5-carboxylate,
 - 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid,
 - methyl 3-allyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2H-1-benzofuran-6-carboxylate,
 - [3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofur-5-oyl]morpholine,

- N-4-hydroxyphenyl-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxamide,
- N-butyl-3-methyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-2H-1-benzofuran-5-carboxamide,
- methyl 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylate,
- 3-[4-(1-adamantyl)-3-methoxyphenyl-3-methyl-2H-1-benzofuran]-6-carboxylic acid,
- methyl 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate,
- 3-(3-methyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylic acid,
- methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylate,
- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(3,5-di-tert-butyl-4-hydroxybenzyl)-2H-1-benzofuran-6-carboxylic acid,
- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-methanol,
- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carbaldehyde,
- methyl (-)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-

carboxylate,

- methyl (+)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-5-carboxylate,

5 - methyl (-)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate,

- methyl (+)-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-methyl-2H-1-benzofuran-6-carboxylate,

10 - methyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylate,

- 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-(2-hexenyl)-2H-1-benzofuran-6-carboxylic acid,

15 - 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-3-hexyl-2H-1-benzofuran-6-carboxylic acid,

- methyl 3-methoxycarbonylmethyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-2H-1-benzofuran-6-carboxylate,

20 - 3-carboxymethyl-3-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-2-naphthyl)-2H-1-benzofuran-6-carboxylic acid.

25 20. Compounds according to Claim 1, characterized in that they have at least one of the following characteristics:

- R_1 is a radical $-(CH_2)_p-CO-O-R_{13}$

- R_2 is a hydrogen
- R_3 is a hydrogen or an alkenyl radical
- R_5 or R_6 is a radical $-OR_{11}$
- R_7 is a cycloalkyl radical
- 5 - Z_1 is an oxygen atom
- Y is a radical $C(R_9)_2$
- m is equal to 1.

21. Compounds according to any one of the preceding claims, for use as medication.

- 10 22. Compounds according to Claim 21, for use as medicinal products intended for the treatment of dermatological complaints associated with a keratinization disorder which has a bearing on differentiation and on proliferation, in particular for
- 15 treating common acnes, comedones, polymorphonuclear leukocytes, acne rosacea, nodulocystic acne, acne conglobata, senile acne, secondary acnes such as solar acne, medication-induced acne or occupational acne; for treating other types of keratinization disorders, in
- 20 particular ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias and leucoplasiform states, cutaneous or mucous (buccal) lichen; for treating other dermatological complaints associated with a keratinization disorder having an
- 25 inflammatory and/or immunoallergic component and, in particular, all forms of psoriasis, whether it is cutaneous, mucous or unguinal psoriasis, and even psoriatic rheumatism, or alternatively cutaneous atopy,

such as eczema, or respiratory atopy or alternatively gingival hypertrophy; the compounds may also be used in certain inflammatory complaints which do not exhibit a disorder of keratinization; for treating all dermal or

5 epidermal proliferations, whether benign or malignant and whether or not they are of viral origin, such as common warts, flat warts and verruciform epidermodysplasia, oral or florid papillomatosis and proliferations which may be induced by ultraviolet

10 radiation, in particular in the case of basocellular and spinocellular epithelioma; for treating other dermatological disorders such as bullosis and collagen diseases; for treating certain ophthalmological disorders, in particular corneopathies; for repairing

15 or combating both light-induced and chronological ageing of the skin or for reducing actinic keratosis and pigmentations, or any pathology associated with chronological or actinic ageing; for preventing or curing the stigmata of epidermal and/or dermal atrophy

20 induced by local or systemic corticosteroids, or any other form of skin atrophy, for preventing or treating cicatrization disorders or for preventing or repairing vibicies; for promoting cicatrization, for combating disorders of sebaceous functioning such as the

25 hyperseborrhoea of acne or simple seborrhoea; for treating or preventing cancerous or precancerous states, more particularly promyelocytic leukaemias; for treating inflammatory complaints such as arthritis, for

treating any complaint of viral origin on the skin or generally; for preventing or treating alopecia; for treating dermatological complaints with an immune component; for treating complaints of the

5 cardiovascular system such as arteriosclerosis or hypertension, as well as insulin-independent diabetes, and for treating skin disorders due to exposure to UV radiation.

23. Pharmaceutical composition,

10 characterized in that it comprises, in a pharmaceutically acceptable support, at least one of the compounds as defined in any one of Claims 1 to 20.

24. Composition according to Claim 23,

15 characterized in that the concentration of compound(s) according to one of Claims 1 to 16 is between 0.001% and 5% by weight relative to the composition as a whole.

25. Cosmetic composition, characterized in that it comprises, in a cosmetically acceptable

20 support, at least one of the compounds as defined in any one of Claims 1 to 20.

26. Composition according to Claim 25,

characterized in that the concentration of compound(s) according to one of Claims 1 to 20 is between 0.001%

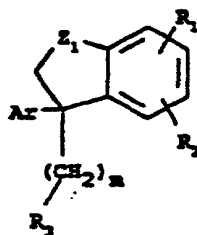
25 and 3% by weight relative to the composition as a whole.

27. Use of a cosmetic composition as defined in either of Claims 25 and 26, for body or hair hygiene.

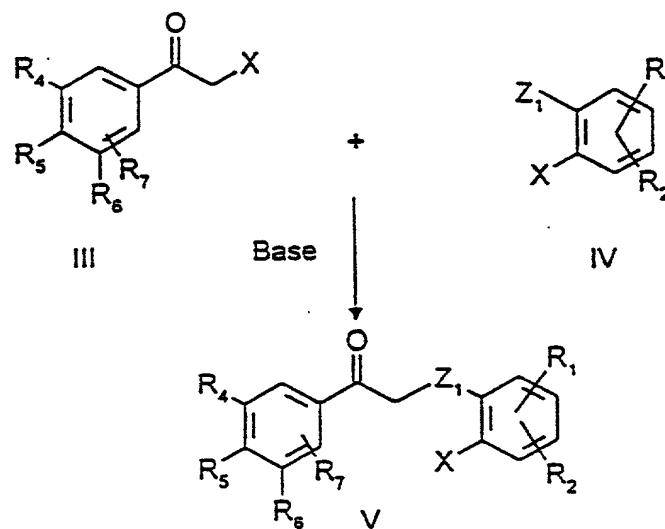
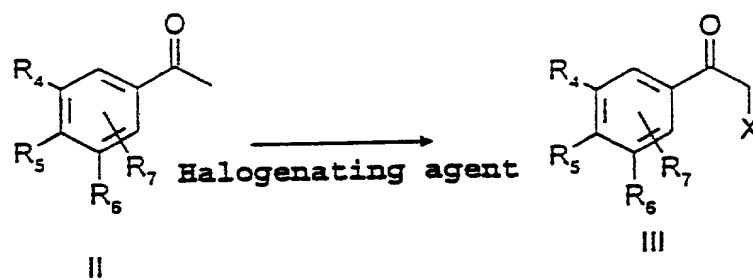
ABSTRACT

HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF

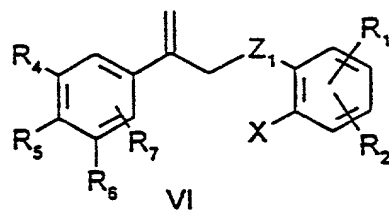
The invention relates to novel heterocyclic biaryl compounds which have the general formula (I):



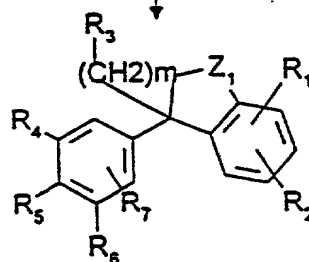
as well as to the use of these compounds in pharmaceutical compositions intended for use in human or veterinary medicine (dermatological, rheumatic, respiratory, cardiovascular and ophthalmological complaints in particular), or alternatively in cosmetic compositions.



Phosphine or
phosphonate
Base

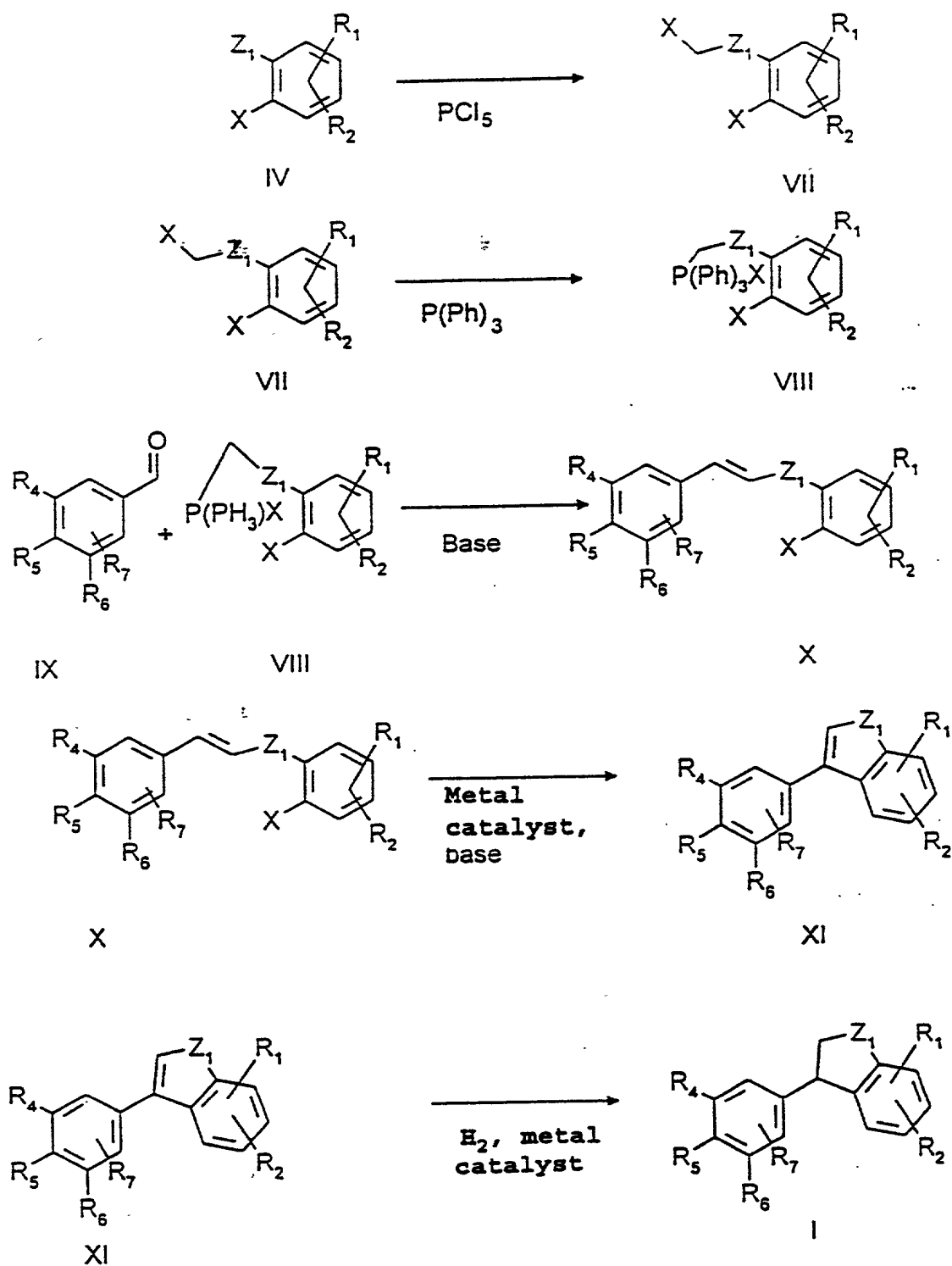


Metal catalyst,
electrophile



X : halogen
 Z_1 : hetero atom
FIGURE 1

2/2



X: halogen
 Z₁: hetero atom

FIGURE 2

5/15/97
COPY

**COMBINED DECLARATION AND POWER OF ATTORNEY
FOR UTILITY PATENT APPLICATION**

Attorney's Docket No.

016800-167

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I BELIEVE I AM THE ORIGINAL, FIRST AND SOLE INVENTOR (if only one name is listed below) OR AN ORIGINAL, FIRST AND JOINT INVENTOR (if more than one name is listed below) OF THE SUBJECT MATTER WHICH IS CLAIMED AND FOR WHICH A PATENT IS SOUGHT ON THE INVENTION ENTITLED:

HETEROCYCLIC BIARYL COMPOUNDS, PHARMACEUTICAL AND

COSMETIC COMPOSITIONS CONTAINING THEM AND USES THEREOF

the specification of which

(check one)

☐

is attached hereto;

☒

was filed on 04 February 1997 as

International Application No. PCT/FR97/00217

and was amended on _____;
(if applicable)

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE;

I ACKNOWLEDGE THE DUTY TO DISCLOSE TO THE OFFICE ALL INFORMATION KNOWN TO ME TO BE MATERIAL TO PATENTABILITY AS DEFINED IN TITLE 37, CODE OF FEDERAL REGULATIONS, Sec. 1.56 (as amended effective March 16, 1992);

I do not know and do not believe the said invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application; that said invention was not in public use or on sale in the United States of America more than one year prior to said application; that said invention has not been patented or made the subject of an inventor's certificate issued before the date of said application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than twelve months prior to said application;

I hereby claim foreign priority benefits under Title 35, United States Code Sec. 119 and/or Sec. 365 of any foreign application(s) for patent or inventor's certificate as indicated below and have also identified below any foreign application for patent or inventor's certificate on this invention having a filing date before that of the application(s) on which priority is claimed:

COMBINED DECLARATION AND POWER OF ATTORNEY			Attorney's Docket No. 010315-025																																																																								
COUNTRY/INTERNATIONAL	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED																																																																								
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			YES <u> </u> NO <u> </u>																																																																								
<p>I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 33%;">William L. Mathis</td> <td style="width: 10%; text-align: right;">17,337</td> <td style="width: 33%;">Ralph L. Freeland, Jr.</td> <td style="width: 10%; text-align: right;">16,110</td> <td style="width: 33%;">William C. Rowland</td> <td style="width: 10%; text-align: right;">30,888</td> </tr> <tr> <td>Peter H. Smolka</td> <td style="text-align: right;">15,913</td> <td>Robert G. Mukai</td> <td style="text-align: right;">28,531</td> <td>T. Gene Dillahunt</td> <td style="text-align: right;">25,423</td> </tr> <tr> <td>Robert S. Swecker</td> <td style="text-align: right;">19,885</td> <td>George A. Hovanec, Jr.</td> <td style="text-align: right;">28,223</td> <td>Anthony W. Shaw</td> <td style="text-align: right;">30,104</td> </tr> <tr> <td>Platon N. Mandros</td> <td style="text-align: right;">22,124</td> <td>James A. LaBarre</td> <td style="text-align: right;">28,632</td> <td>Patrick C. Keane</td> <td style="text-align: right;">32,858</td> </tr> <tr> <td>Benton S. Duffett, Jr.</td> <td style="text-align: right;">22,030</td> <td>E. Joseph Gess</td> <td style="text-align: right;">28,510</td> <td>Bruce J. Boggs, Jr.</td> <td style="text-align: right;">32,344</td> </tr> <tr> <td>Joseph R. Magnone</td> <td style="text-align: right;">24,239</td> <td>R. Danny Huntington</td> <td style="text-align: right;">27,903</td> <td>William H. Benz</td> <td style="text-align: right;">25,952</td> </tr> <tr> <td>Norman H. Stepno</td> <td style="text-align: right;">22,716</td> <td>Eric H. Weisblatt</td> <td style="text-align: right;">30,505</td> <td>Peter K. Skiff</td> <td style="text-align: right;">31,917</td> </tr> <tr> <td>Ronald L. Grudziecki</td> <td style="text-align: right;">24,970</td> <td>James W. Peterson</td> <td style="text-align: right;">26,057</td> <td>Richard J. McGrath</td> <td style="text-align: right;">29,195</td> </tr> <tr> <td>Frederick G. Michaud, Jr.</td> <td style="text-align: right;">26,003</td> <td>Teresa Stanek Rea</td> <td style="text-align: right;">30,427</td> <td>Matthew L. Schneider</td> <td style="text-align: right;">32,814</td> </tr> <tr> <td>Alan E. Kopecki</td> <td style="text-align: right;">25,813</td> <td>Robert E. Krebs</td> <td style="text-align: right;">25,885</td> <td>Michael G. Savage</td> <td style="text-align: right;">32,596</td> </tr> <tr> <td>Regis E. Slutter</td> <td style="text-align: right;">26,999</td> <td>Robert M. Schulman</td> <td style="text-align: right;">31,196</td> <td>Gerald F. Swiss</td> <td style="text-align: right;">30,113</td> </tr> <tr> <td>Samuel C. Miller, III</td> <td style="text-align: right;">27,360</td> <td></td> <td></td> <td></td> <td></td> </tr> </table>				William L. Mathis	17,337	Ralph L. Freeland, Jr.	16,110	William C. Rowland	30,888	Peter H. Smolka	15,913	Robert G. Mukai	28,531	T. Gene Dillahunt	25,423	Robert S. Swecker	19,885	George A. Hovanec, Jr.	28,223	Anthony W. Shaw	30,104	Platon N. Mandros	22,124	James A. LaBarre	28,632	Patrick C. Keane	32,858	Benton S. Duffett, Jr.	22,030	E. Joseph Gess	28,510	Bruce J. Boggs, Jr.	32,344	Joseph R. Magnone	24,239	R. Danny Huntington	27,903	William H. Benz	25,952	Norman H. Stepno	22,716	Eric H. Weisblatt	30,505	Peter K. Skiff	31,917	Ronald L. Grudziecki	24,970	James W. Peterson	26,057	Richard J. McGrath	29,195	Frederick G. Michaud, Jr.	26,003	Teresa Stanek Rea	30,427	Matthew L. Schneider	32,814	Alan E. Kopecki	25,813	Robert E. Krebs	25,885	Michael G. Savage	32,596	Regis E. Slutter	26,999	Robert M. Schulman	31,196	Gerald F. Swiss	30,113	Samuel C. Miller, III	27,360				
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<p>and: _____</p> <p>Address all correspondence to: Norman H. Stepno Burns, Doane, Swecker & Mathis, LLP P.O. Box 1404 Alexandria, Virginia 22313-1404</p> <p>Address all telephone calls to: <u>Norman H. Stepno</u> at (703) 836-6620.</p> <p>I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.</p>																																																																											
FULL NAME OF SOLE OR FIRST INVENTOR		SIGNATURE	DATE																																																																								
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